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See application file for complete search history.

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(57) **ABSTRACT**

This disclosure relates to binding agents with specificity for programmed cell death 1 (PD-1) and to methods for using the same to treat, prevent and/or ameliorate an infectious disease (e.g., human immunodeficiency virus (HIV)), cancer and/or autoimmunity. In addition, this disclosure identifies a novel binding patch ("P2") on PD-1 that is linked with a previously unidentified functional activity of PD-1 that is distinct from the interaction site involved with either the PD-L1 or PD-L2 ligands. Furthermore, we demonstrate that antibodies that interact with this region of PD-1 are able to act as antagonists of PD-1 and that this antagonism is further enhanced with the addition of antibodies that act through the blockade of the PD-1/PD-L1/L2 interaction.

15 Claims, 32 Drawing Sheets

Specification includes a Sequence Listing.

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* cited by examiner

FIG. 1A

Mouse PD-1 (GenBank Accession No. CAA48113.1; Ishida, et al. EMBO J. 11(11) : 3887-3895 (1992))

```
1    mwvrqvpwsf twavlqlswq sgwllevpng pwrsltfypa wltvsegana tftcslsnws
61  edlmlnwnrl spsnqtekqa afcnglsqpv qdarfqiiql pnrhdfhmni ldtrrndsgi
121 ylcgaislhp kakieespga elvvterile tstrypspsp kpegrfqgmv igimsalvgi
181 pvllllawal avfcstsmse argagskddt lkeepsaapv psvayeeldf qgrektpelp
241 tacvhteyat ivfteglgas amgrrgsadg lqgprpprhe dghcswpl
(SEQ ID NO.:140)
```

FIG. 1B

Human PD-1 (GenBank Accession No. AAC51773.1; Finger, et al. Gene 197(1-2): 177-187 (1997))

```
1   mqipqapwpv vwavlqlgwr pgwfldspdr pwnpptffpa llvvtegdna tftcsfsnts
61  esfvlnwyrm spsnqtdkla afpedrsqpg qdcrfrvtql pngrdfhmsv vrarrndsgt
121 ylcgaislap kaqikeslra elrvterrae vptahpspsp rpagqfqtlv vgvvggllgs
181 lvllvwvlav icsraargti garrtgqplk edpsavpvfs vdygeldfqw rektpeppvp
241 cvpeqteyat ivfpsgmgts sparrgsadg prsaqplrpe dghcswpl
(SEQ ID NO.:141)
```

FIG. 2

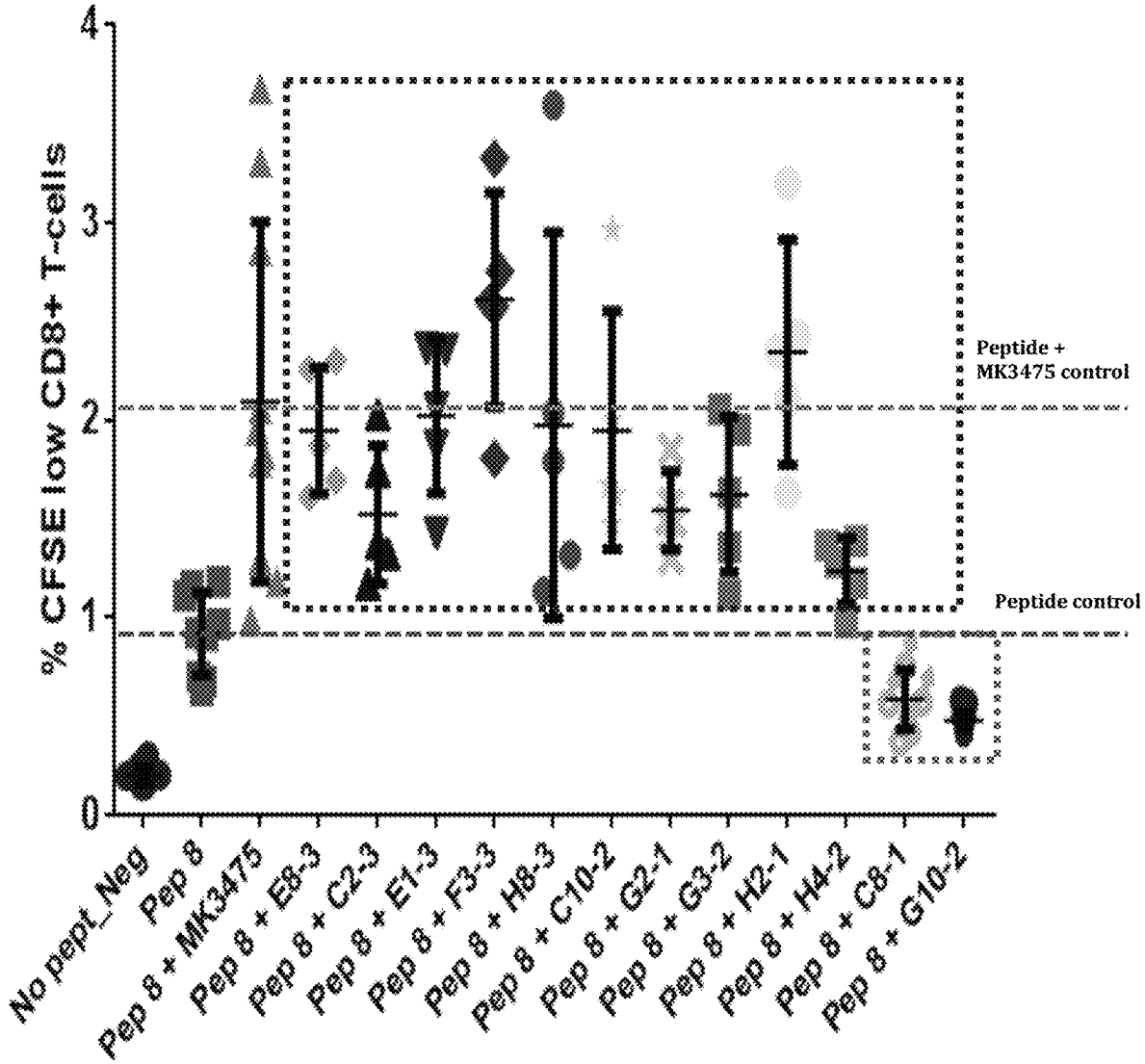

% CFSE low CD8+ T-cells
0
1
2
3
4
Peptide + MK3475 control
Peptide control
No pept_Neg
Pep 8
Pep 8 + MK3475
Pep 8 + E8-3
Pep 8 + C2-3
Pep 8 + E1-3
Pep 8 + F3-3
Pep 8 + H8-3
Pep 8 + C10-2
Pep 8 + G2-1
Pep 8 + G3-2
Pep 8 + H2-1
Pep 8 + H4-2
Pep 8 + C8-1
Pep 8 + G10-2

FIG. 3

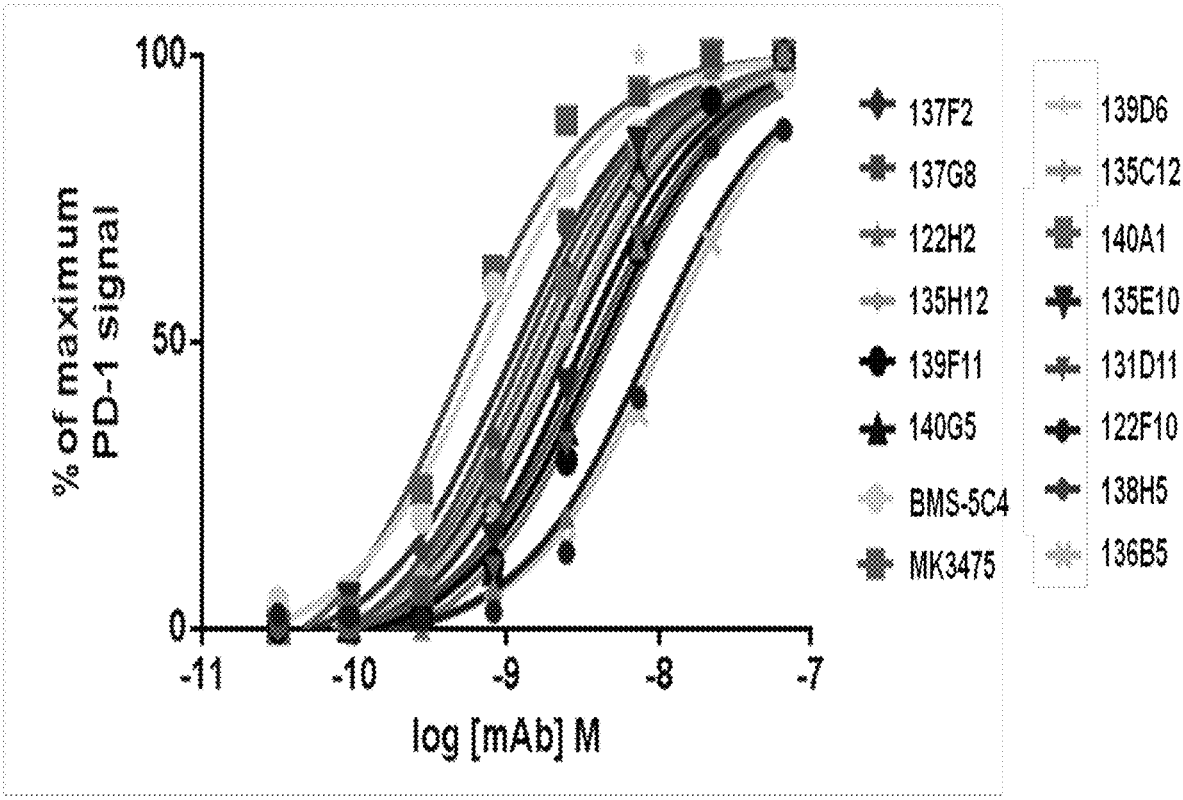

100
50
0
% of maximum PD-1 signal
-11
-10
-9
-8
-7
log [mAb] M
137F2
137G8
122H2
135H12
139F11
140G5
BMS-5C4
MK3475
139D6
135C12
140A1
135E10
131D11
122F10
138H5
136B5

FIG. 4

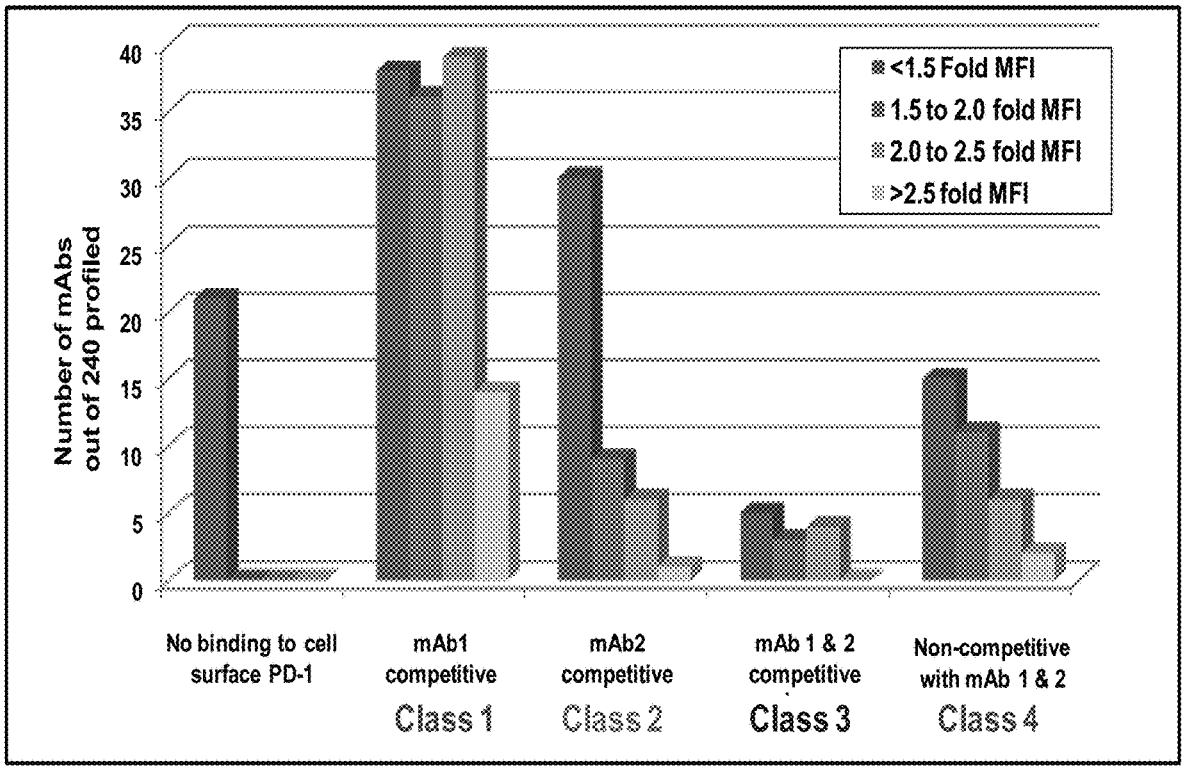

Number of mAbs out of 240 profiled
40
35
30
25
20
15
10
5
0
<1.5 Fold MFI
1.5 to 2.0 fold MFI
2.0 to 2.5 fold MFI
>2.5 fold MFI
No binding to cell surface PD-1
mAb1 competitive
Class 1
mAb2 competitive
Class 2
mAb 1 & 2 competitive
Class 3
Non-competitive with mAb 1 & 2
Class 4

FIG. 5A

Antibody concentration response curves for the inhibition of PD-1 / PD-L1 interaction

Class 1 mAb 137F2: Strongly competitive

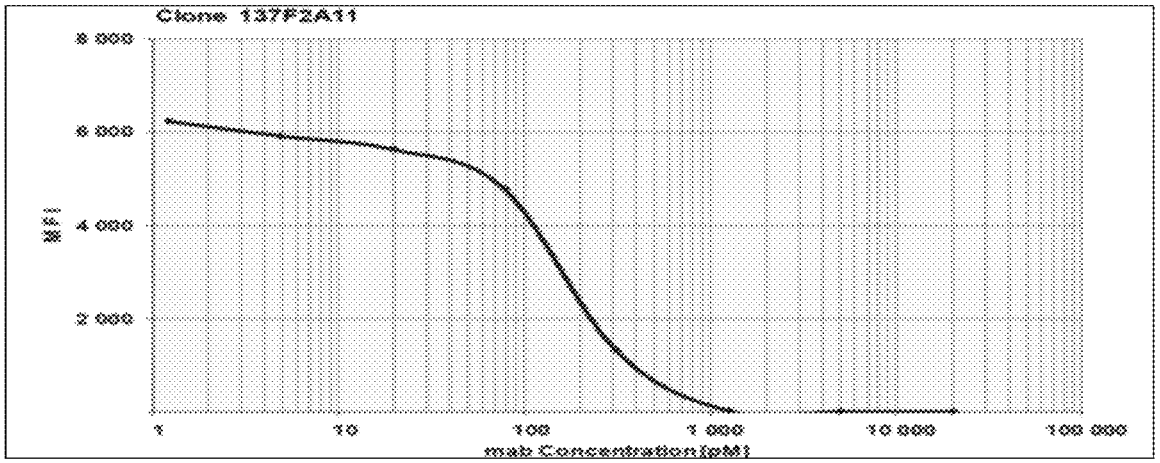


FIG. 5B

Antibody concentration response curves for the inhibition of PD-1 / PD-L1 interaction

Class 2 mAb 139D6: Partially competitive

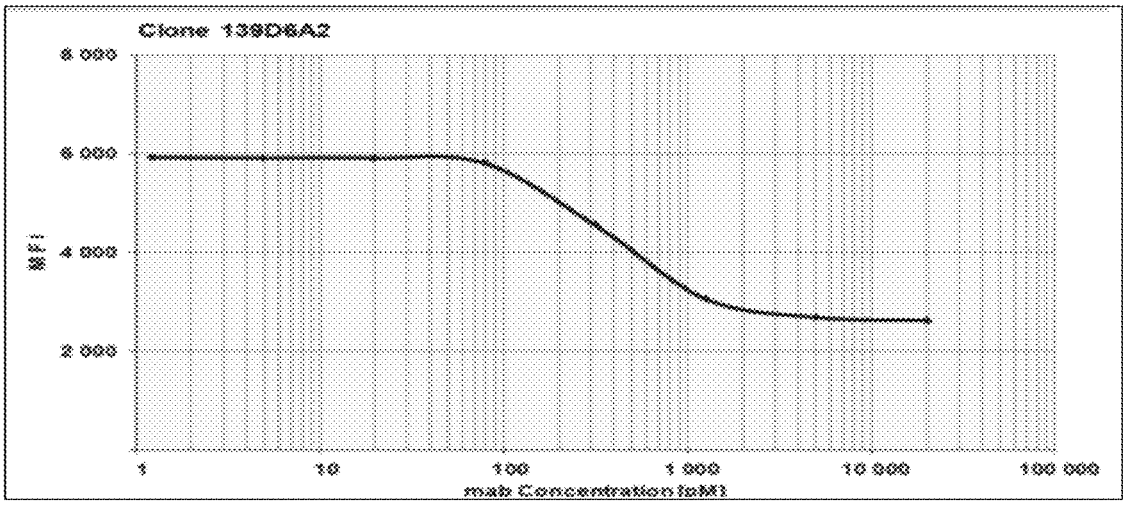


FIG. 5C

Antibody concentration response curves for the inhibition of PD-1 / PD-L1 interaction

Class 2 mAb 136B4: Non-competitive

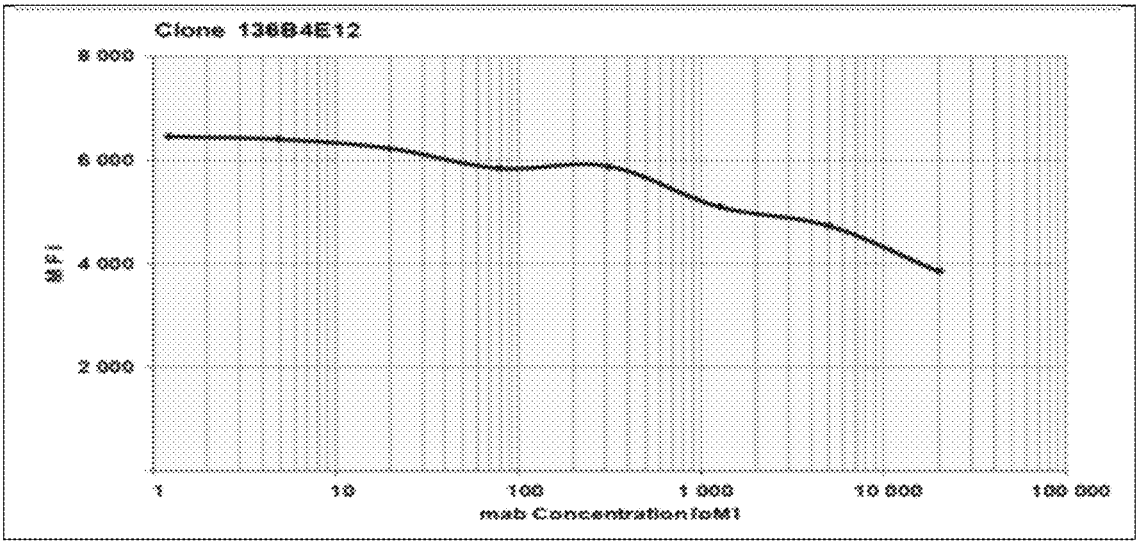


FIG. 5D

Concentration response curves
Binding of human PD-L1 to human PD-1 Fc

Class 1 mAb 137F2: Strongly competitive

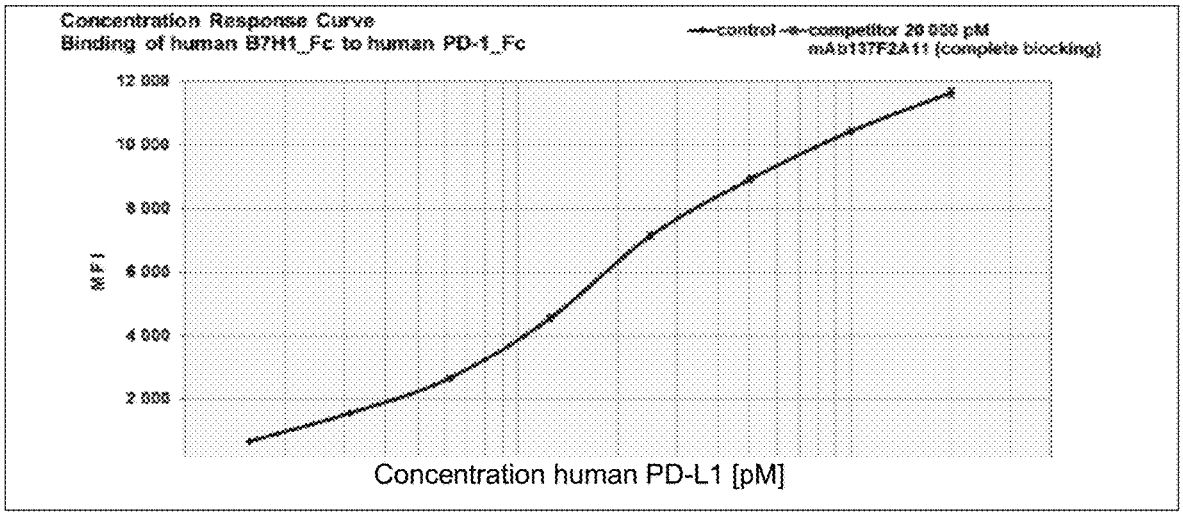


FIG. 5E

Concentration response curves
Binding of human PD-L1 to human PD-1 Fc

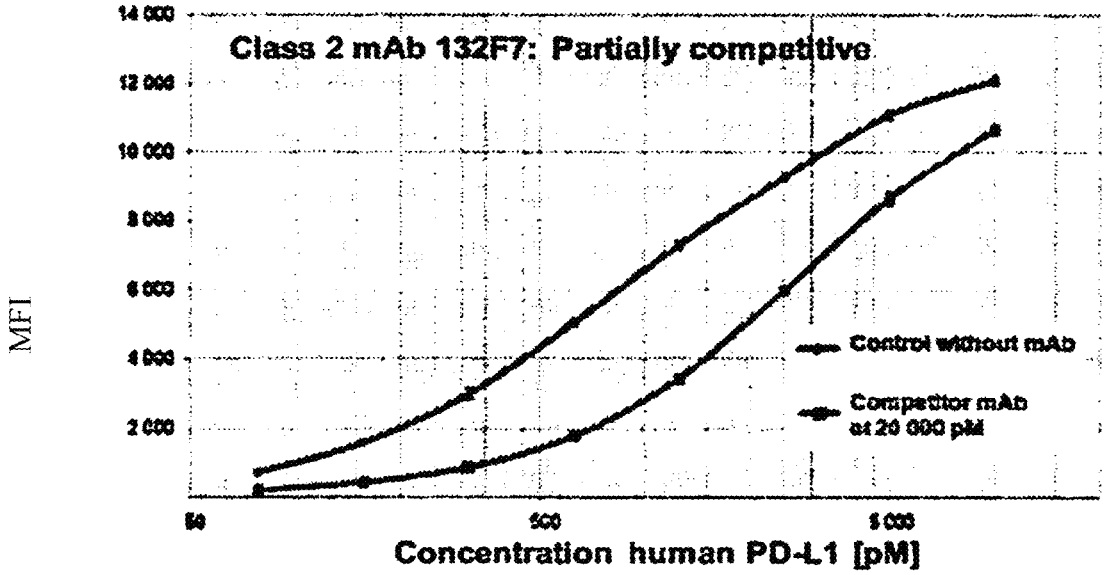


FIG. 5F

Concentration response curves
Binding of human PD-L1 to human PD-1 Fc

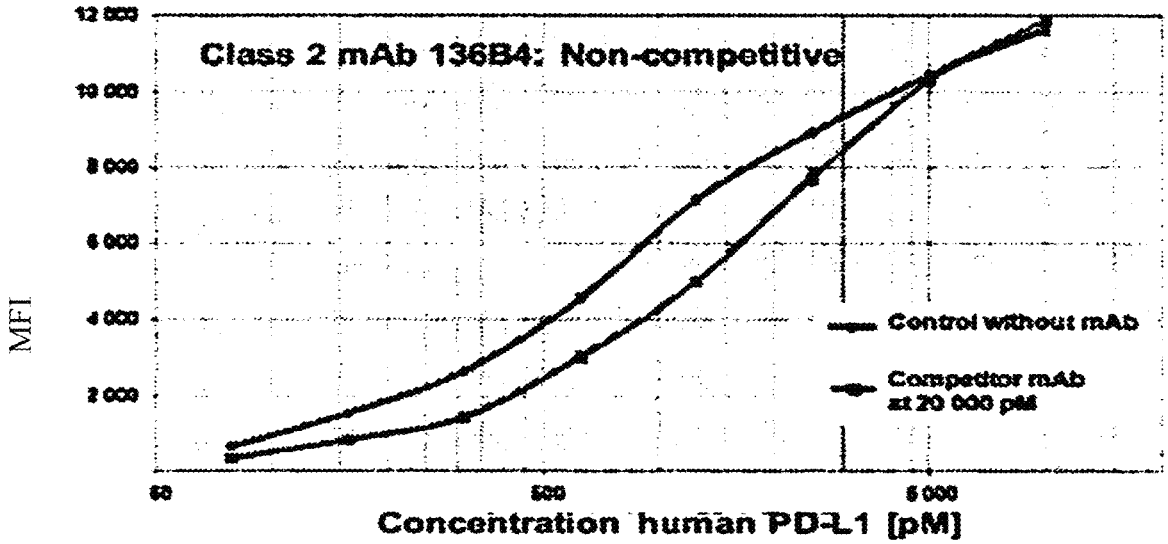


FIG. 6A

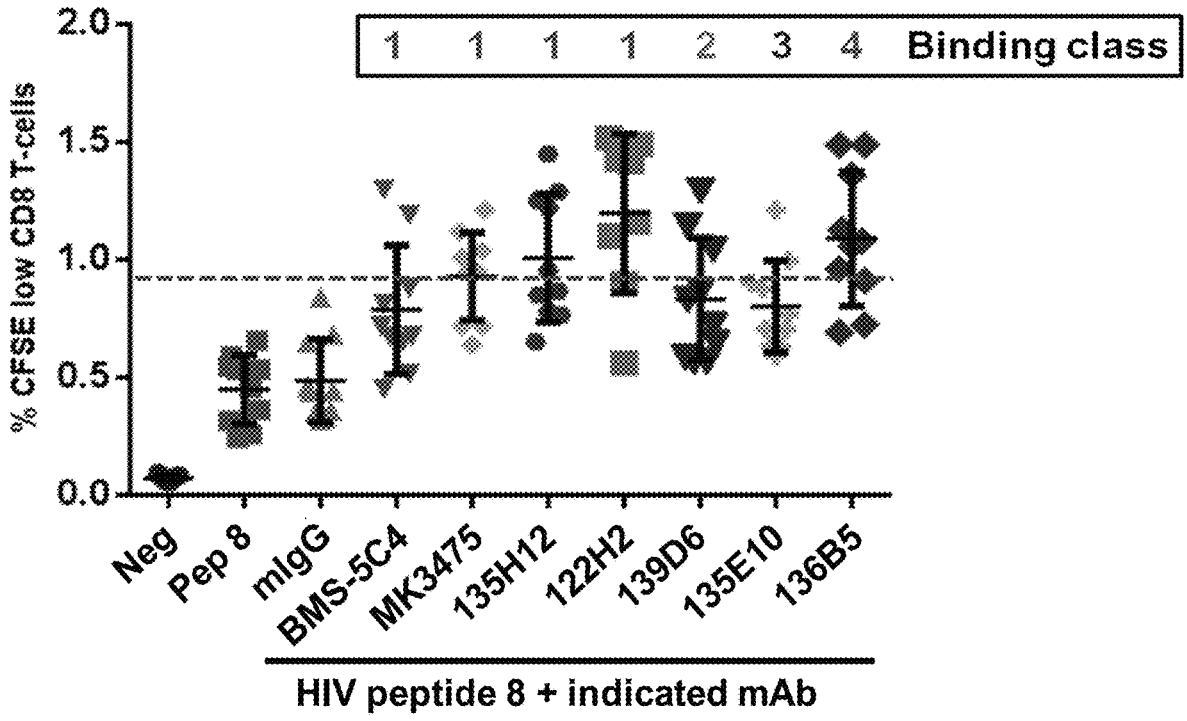

1 1 1 1 2 3 4 Binding class
% CFSE low CD8 T-cells
2.0
1.5
1.0
0.5
0.0
Neg
Pep 8
mIgG
BMS-5C4
MK3475
135H12
122H2
139D6
135E10
136B5
HIV peptide 8 + indicated mAb

FIG. 6B

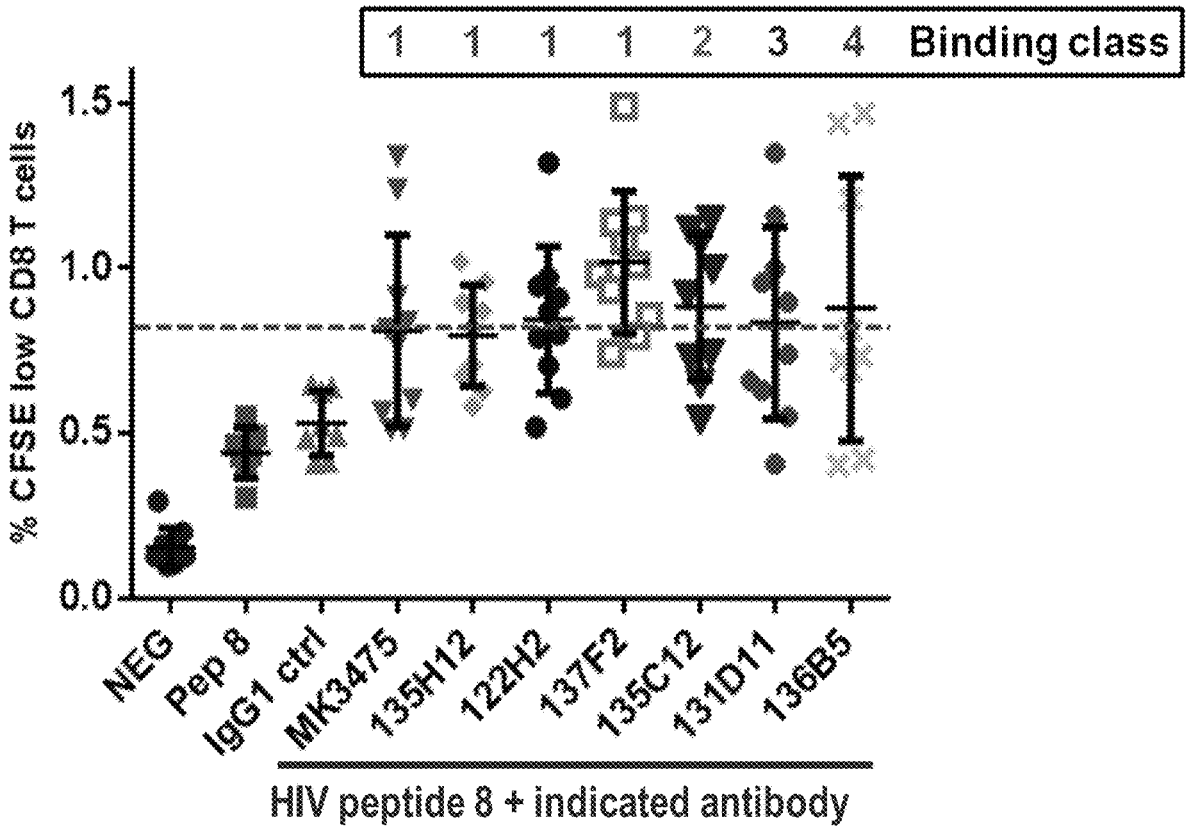

1 1 1 1 2 3 4 Binding class
% CFSE low CD8 T cells
1.5
1.0
0.5
0.0
NEG
Pep 8
IgG1 ctrl
MK3475
135H12
122H2
137F2
135C12
131D11
136B5
HIV peptide 8 + indicated antibody

FIG. 7

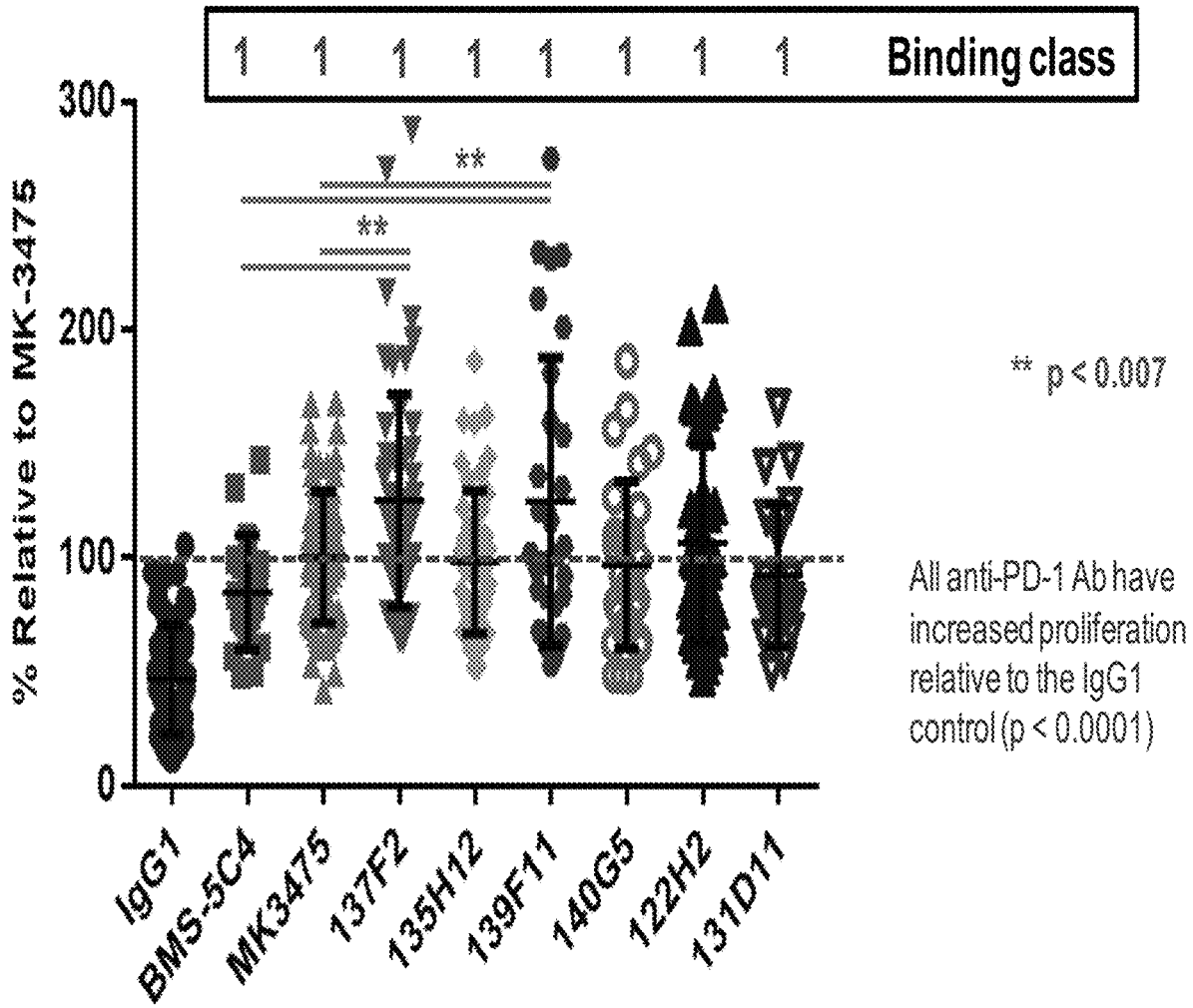

Binding class
1 1 1 1 1 1 1 1
% Relative to MK-3475
300
200
100
0
**
**
IgG1
BMS-5C4
MK3475
137F2
135H12
139F11
140G5
122H2
131D11
** p < 0.007
All anti-PD-1 Ab have increased proliferation relative to the IgG1 control (p < 0.0001)

FIG. 8

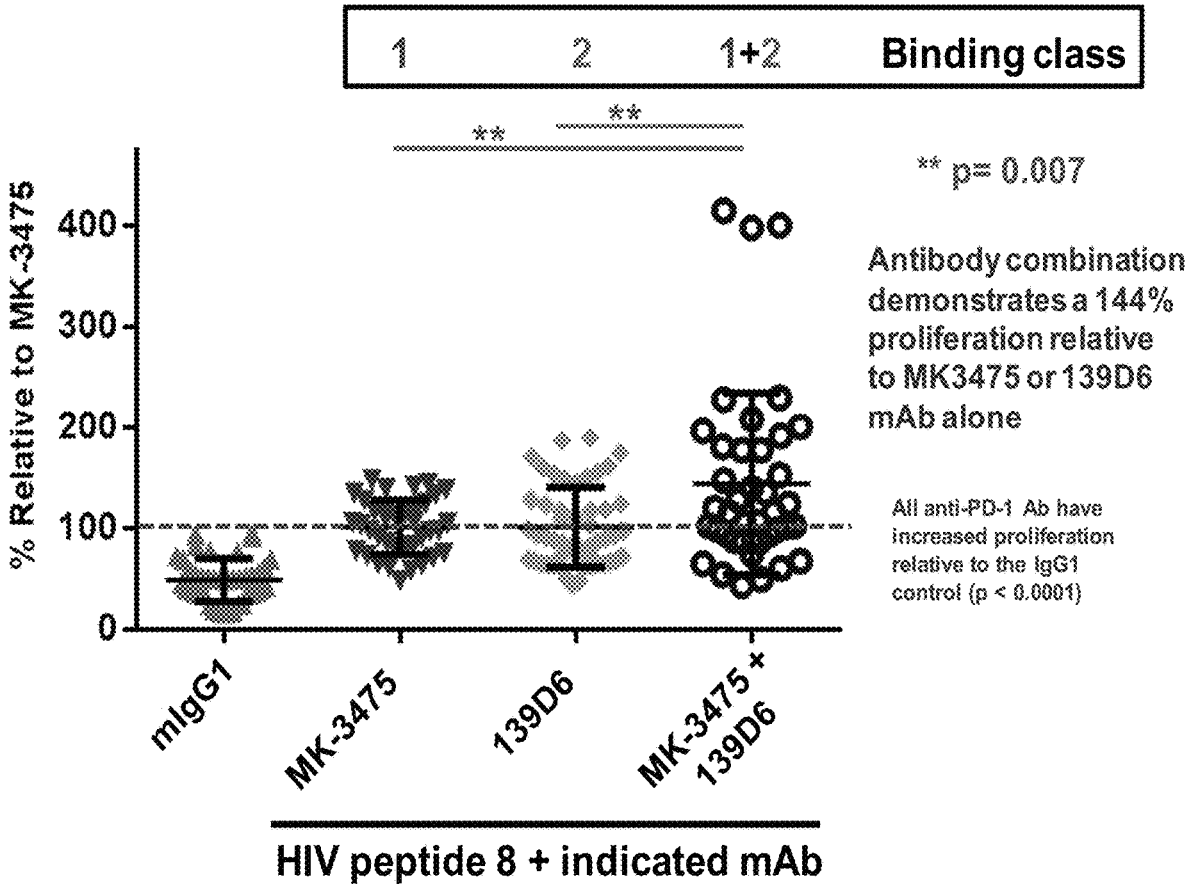

1
2
1+2
Binding class
**
**
** p= 0.007
Antibody combination demonstrates a 144% proliferation relative to MK3475 or 139D6 mAb alone
All anti-PD-1 Ab have increased proliferation relative to the IgG1 control (p < 0.0001)
% Relative to MK-3475
400
300
200
100
0
mIgG1
MK-3475
139D6
MK-3475 + 139D6
HIV peptide 8 + indicated mAb

FIG. 9

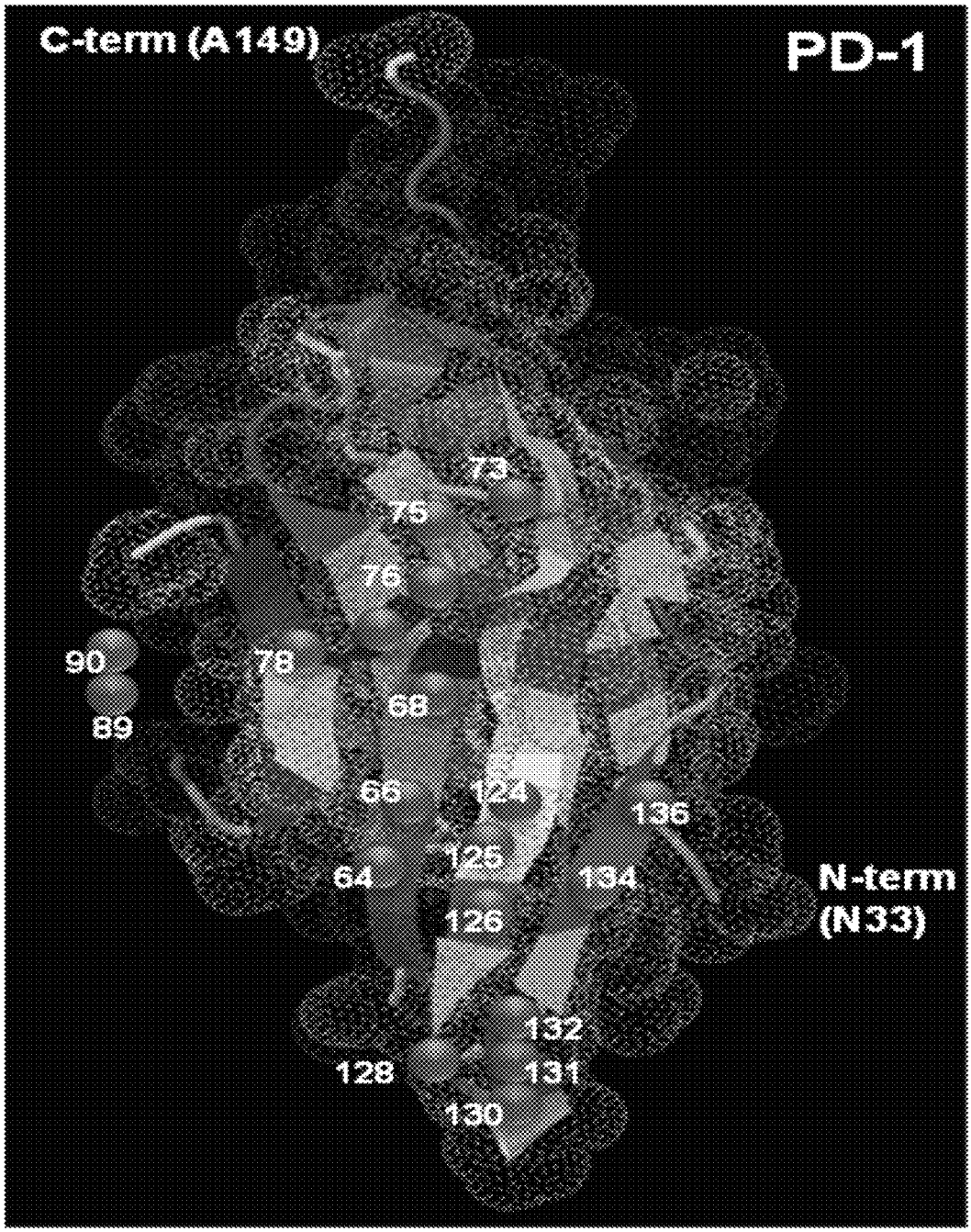

C-term (A149)
PD-1
73
75
76
90
78
68
89
66
124
136
125
64
134
N-term
(N33)
126
132
128
131
130

FIG. 10A

Modifications to PD-1 (SEQ ID NO. 204)

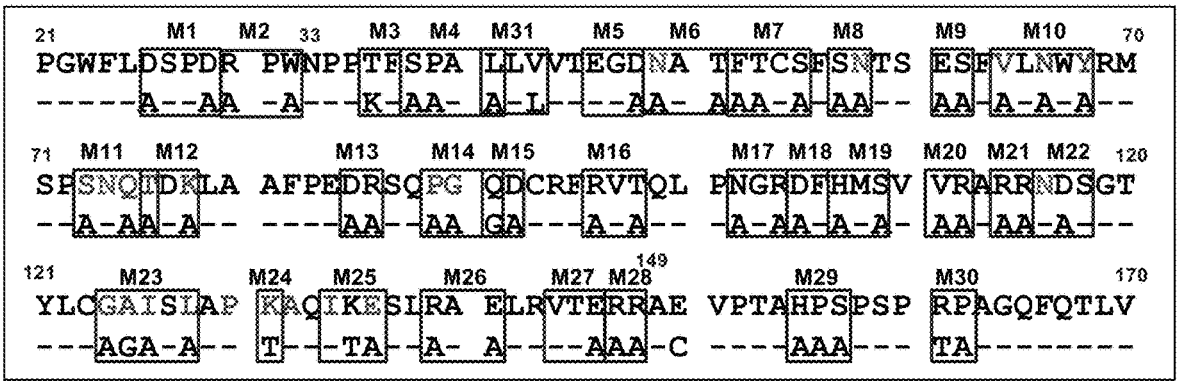


FIG. 10B

Human PD-1 Mutants (modifications highlighted in bold)

1. M1

1 MQIPQAPWPV VWAVLQLGWR PGWFL**A**SP**A**R PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS
61 ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT
121 YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 139)

2. M2

1 MQIPQAPWPV VWAVLQLGWR PGWFLDSPD**A** P**A**NPPTFSPA LLVVTEGDNA TFTCSFSNTS
61 ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT
121 YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 140)

3. M3

1 MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPP**K**FSPA LLVVTEGDNA TFTCSFSNTS
61 ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT
121 YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 141)

4. M4

1 MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPPTF**AA**A **A**LVVTEGDNA TFTCSFSNTS
61 ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT
121 YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 142)

FIG. 10C

5. M5

```
1   MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPPTFSPA LLVVTEGANA TFTCSFSNTS
61  ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT
121 YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 143)
```

6. M6

```
1   MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPPTFSPA LLVVTEGDAA AFTCSFSNTS
61  ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT
121 YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 144)
```

7. M7

```
1   MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TAACAFSNTS
61  ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT
121 YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 145)
```

8. M8

```
1   MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFAATS
61  ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT
121 YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 146)
```

9. M9

```
1   MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS
61  AAFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT
121 YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 147)
```

10. M10

```
1   MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS
61  ESFALAWARM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT
121 YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 148)
```

FIG. 10D

11. M11

```
1   MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS
61  ESFVLNWYRM SPANAADKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT
121 YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 149)
```

12. M12

```
1   MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS
61  ESFVLNWYRM SPSNQADALA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT
121 YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 150)
```

13. M13

```
1   MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS
61  ESFVLNWYRM SPSNQTDKLA AFPEAASQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT
121 YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 151)
```

14. M14

```
1   MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS
61  ESFVLNWYRM SPSNQTDKLA AFPEDRSQAA GDCRFRVTQL PNGRDFHMSV VRARRNDSGT
121 YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 152)
```

15. M15

```
1   MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS
61  ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG AACRFRVTQL PNGRDFHMSV VRARRNDSGT
121 YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 153)
```

16. M16

```
1   MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS
61  ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFAVAQL PNGRDFHMSV VRARRNDSGT
121 YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 154)
```

FIG. 10E

17. M17

```
1   MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS
61  ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PAGADFHMSV VRARRNDSGT
121 YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 155)
```

18. M18

```
1   MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS
61  ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRAFHMSV VRARRNDSGT
121 YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 156)
```

19. M19

```
1   MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS
61  ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFAMAV VRARRNDSGT
121 YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 157)
```

20. M20

```
1   MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS
61  ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV AAARRNDSGT
121 YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 158)
```

21. M21

```
1   MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS
61  ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRAAANDSGT
121 YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 159)
```

22. M22

```
1   MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS
61  ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNASGT
121 YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 160)
```

FIG. 10F

23. M23

```
1   MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS
61  ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT
121 YLCAGASAAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 161)
```

24. M24

```
1   MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS
61  ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT
121 YLCGAISLAP TAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 162)
```

25. M25

```
1   MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS
61  ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT
121 YLCGAISLAP KAQITASLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 163)
```

26. M26

```
1   MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS
61  ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT
121 YLCGAISLAP KAQIKESLAA ALRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 164)
```

27. M27

```
1   MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS
61  ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT
121 YLCGAISLAP KAQIKESLRA ELRVTARRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 165)
```

28. M28

```
1   MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS
61  ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT
121 YLCGAISLAP KAQIKESLRA ELRVTEAAAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 166)
```

FIG. 10G

29. M29

```
1   MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS
61  ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT
121 YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAAAAPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 167)
```

30. M30

```
1   MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS
61  ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT
121 YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP AAAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 168)
```

31. M31

```
1   MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPPTFSPA ALLVTEGDNA TFTCSFSNTS
61  ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT
121 YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 206)
```

Figure 10H

Human PD-1 Amino Acid Sequence (accession NM_005018.2)

```
1   MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS
61  ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT
121 YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO. 204)
```

Figure 10I

Rhesus Monkey PD-1 Amino Acid Sequence (accession NM_001114358.1)
(Differences from human PD-1 highlighted in bold)

```
1   MQIPQAPWPV VWAVLQLGWR PGWFLESPDR PWNPPTFSPA LLLVTEGDNA TFTCSFSNAS
61  ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG RDCRFRVTQL PNGRDFHMSV VRARRNDSGT
121 YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQALV VGVVGGLLGS
181 LVLLVWVLAV ICSRAAQGTI EARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPAP
241 CVPEQTEYAT IVFPSGLGTS SPARRGSADG PRSPRPLRPE DGHCSWPL (SEQ ID NO. 205)
```

FIG. 11A

PD-1 WT

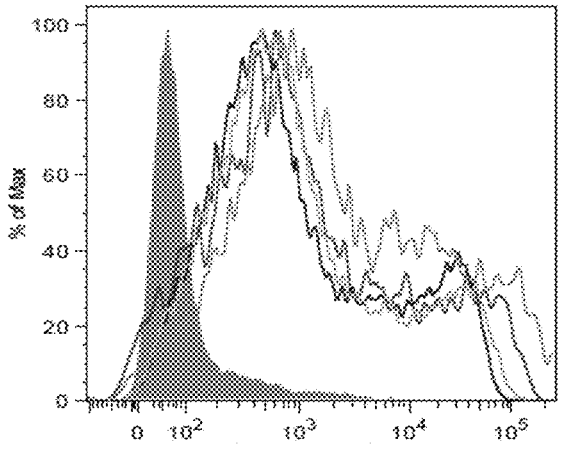
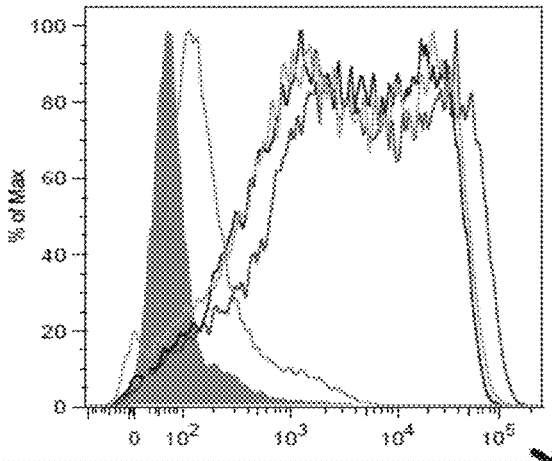


FIG. 11B

PD-1 M13



PE-labeled anti-mouse IgG secondary Ab

FIG. 11C

PD-1 M14

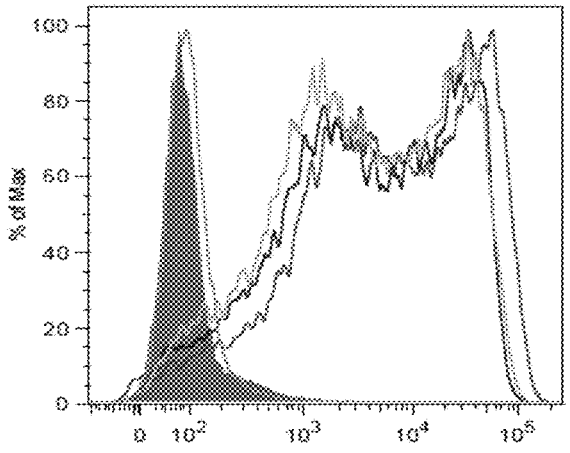
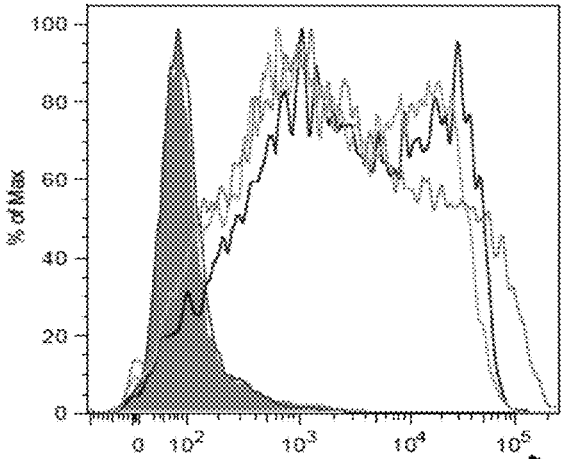


FIG. 11D

PD-1 M23



PE-labeled anti-mouse IgG secondary Ab

MK3475 (Comp)
136B4 (Non-comp)
135C12 (Non-comp)
137F2 (Comp)
IgG1 control

FIG. 12A

PD-1 WT

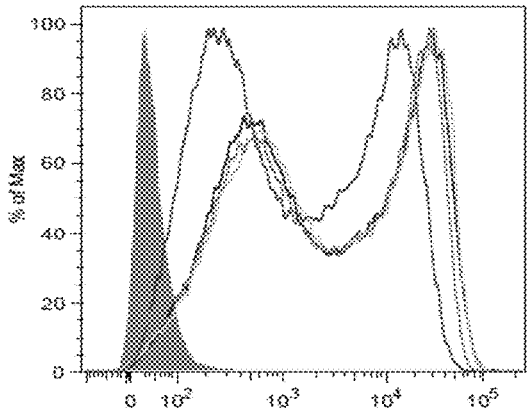
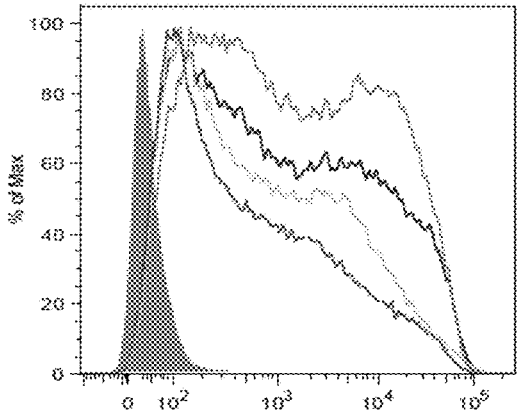


FIG. 12B

PD-1 M13



PE-labeled anti-mouse IgG secondary Ab

FIG. 12C

PD-1 M23

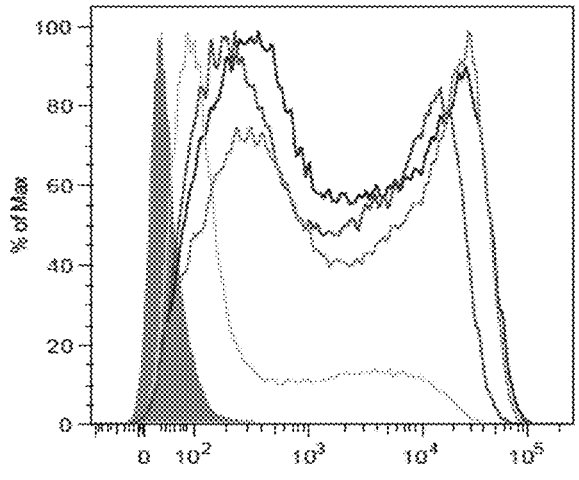
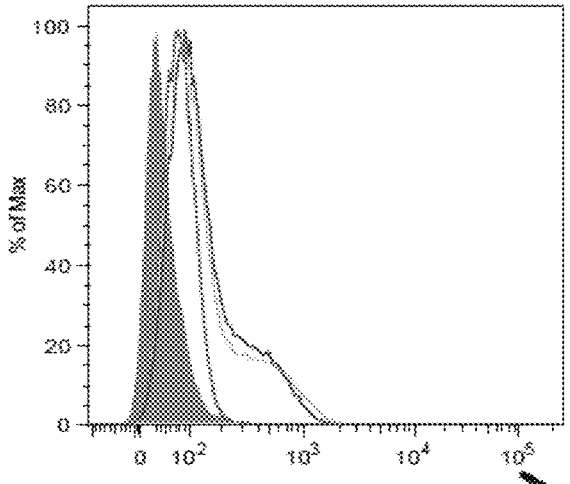


FIG. 12D

PD-1 M4



PE-labeled anti-mouse IgG secondary Ab

135C12 (Non-comp)
134D2 (Comp)
139F11 (Comp)
135D1 (Non-comp)
IgG1 control

FIG. 13A
PD-1 WT

FIG. 13A
PD-1 M31

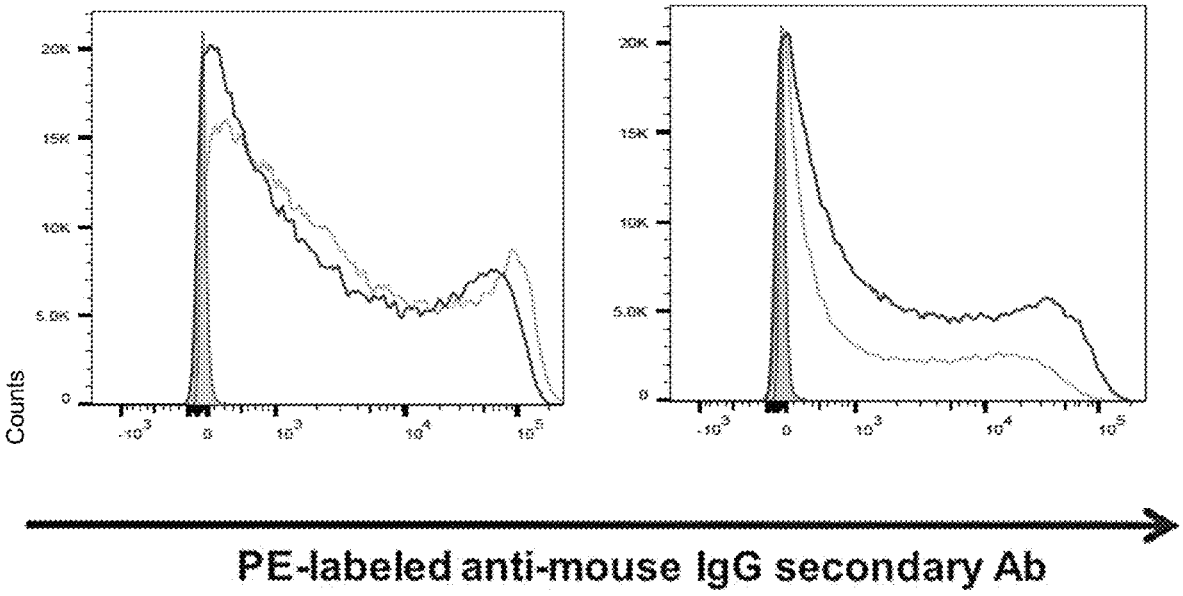


FIG. 13C
PD-1 M5

FIG. 13D
PD-1 M18

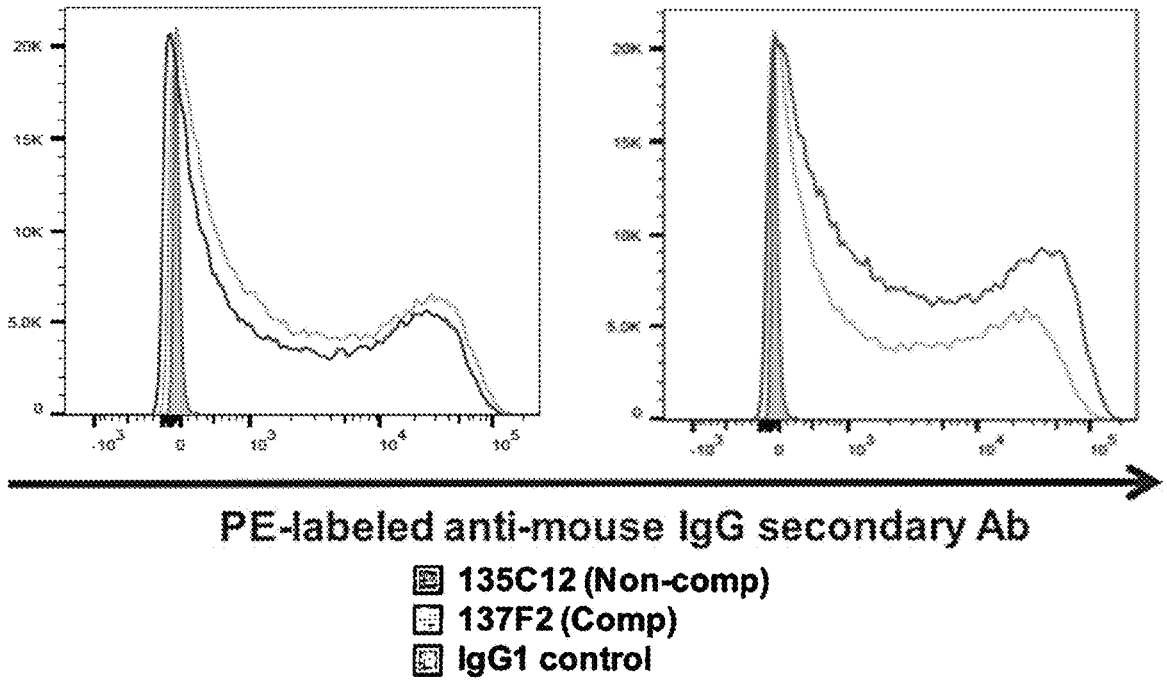


FIG. 14A (WT)

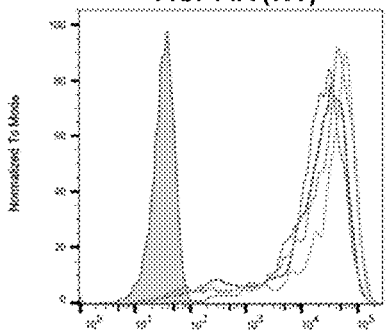
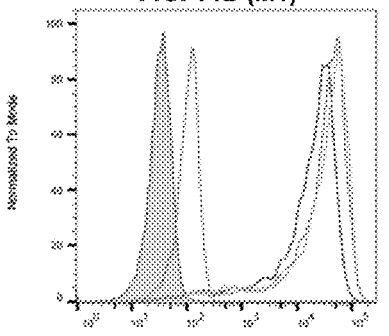


FIG. 14B (M1)



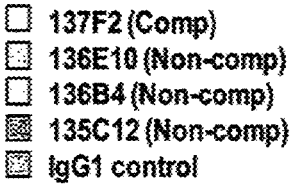


FIG. 14C (M9)

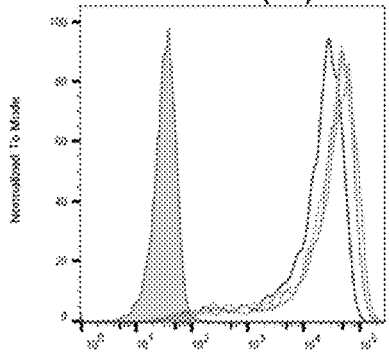


FIG. 14D (M13)

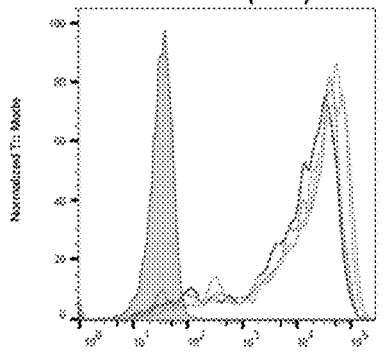


FIG. 14E (M17)

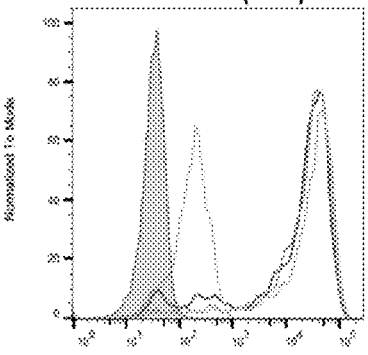


FIG. 14F (M18)

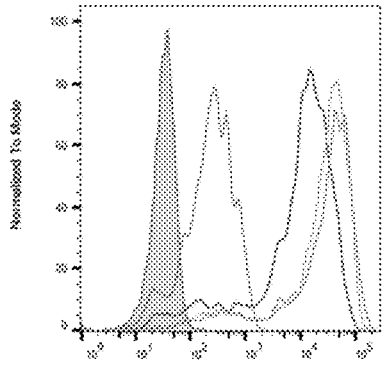


FIG. 14G (M23)

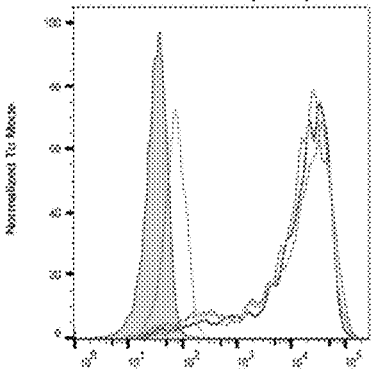


FIG. 14H (M28)

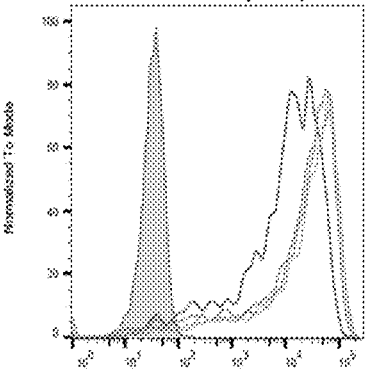


FIG. 15

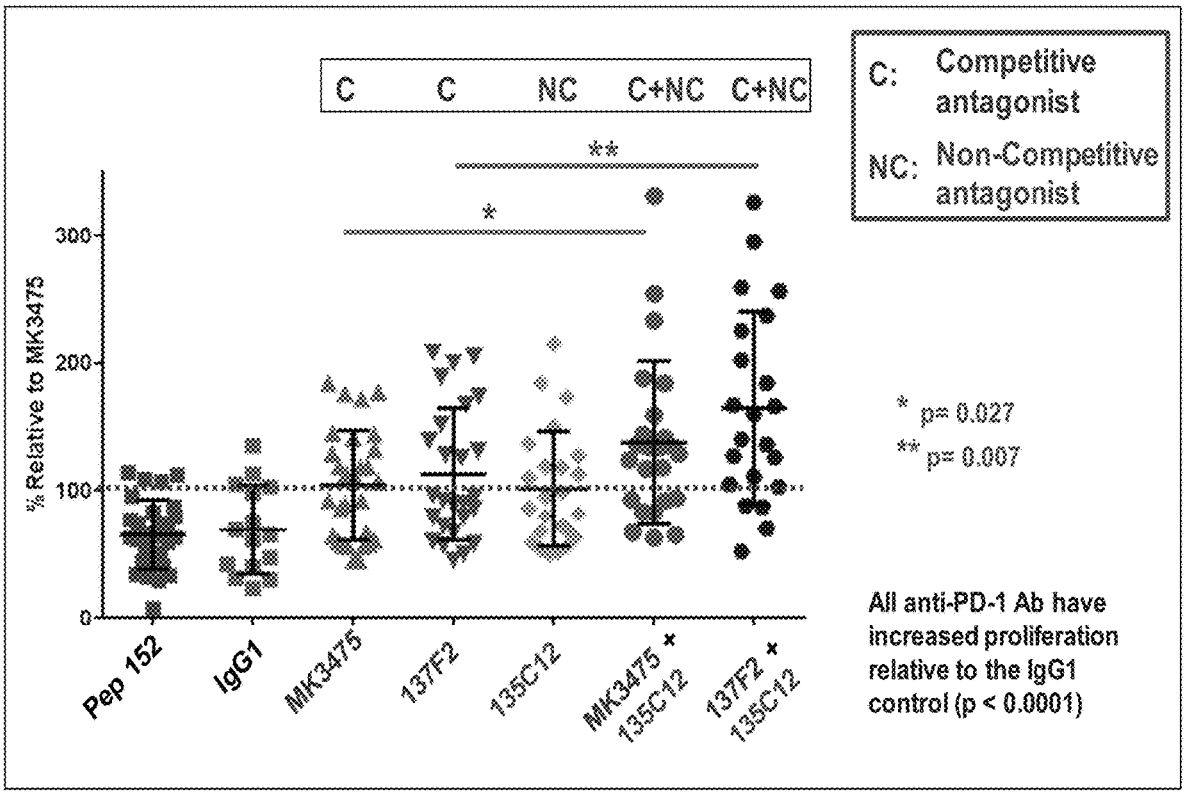

C C NC C+NC C+NC
C: Competitive antagonist
NC: Non-Competitive antagonist
**
*
% Relative to MK3475
300
200
100
0
Pep 152
IgG1
MK3475
137F2
135C12
MK3475 * 135C12
137F2 * 135C12
* p= 0.027
** p= 0.007
All anti-PD-1 Ab have increased proliferation relative to the IgG1 control (p < 0.0001)

FIG. 16A

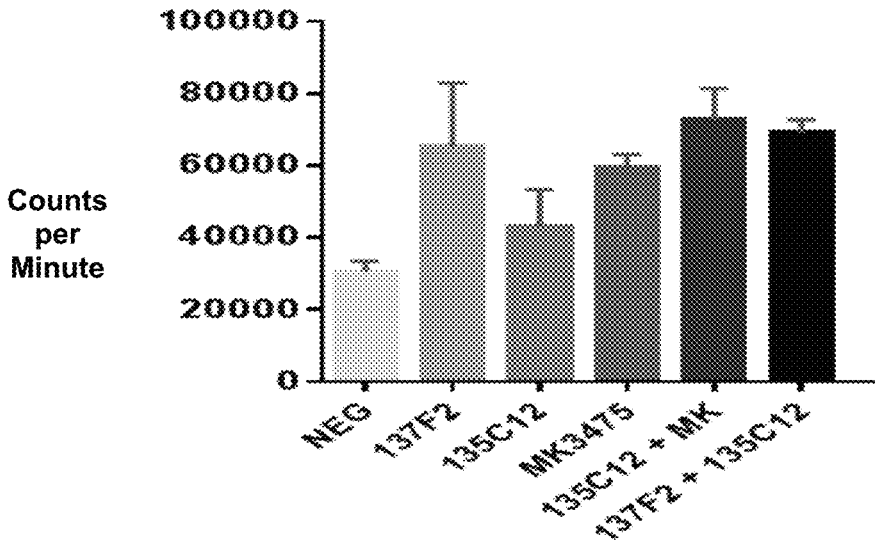


FIG. 16B

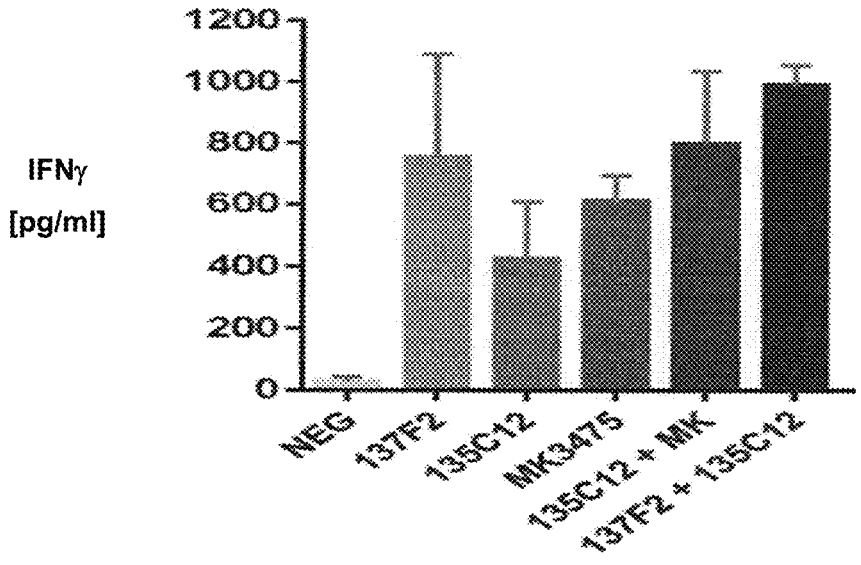
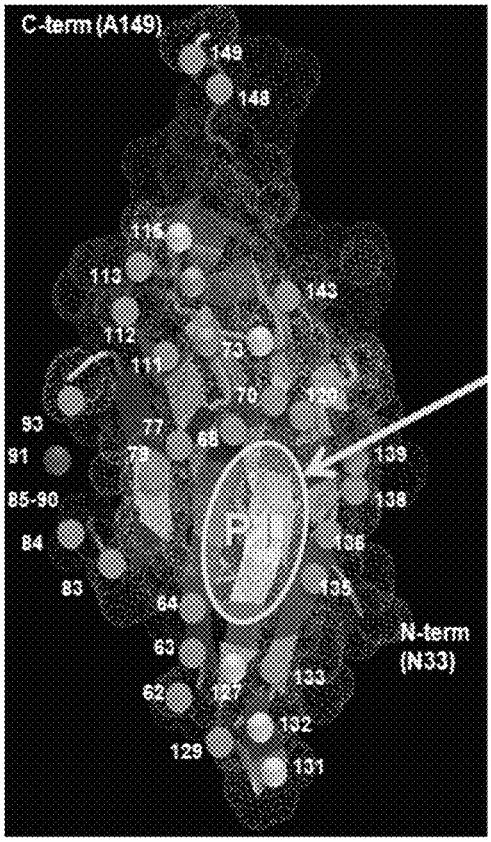
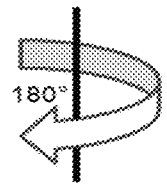


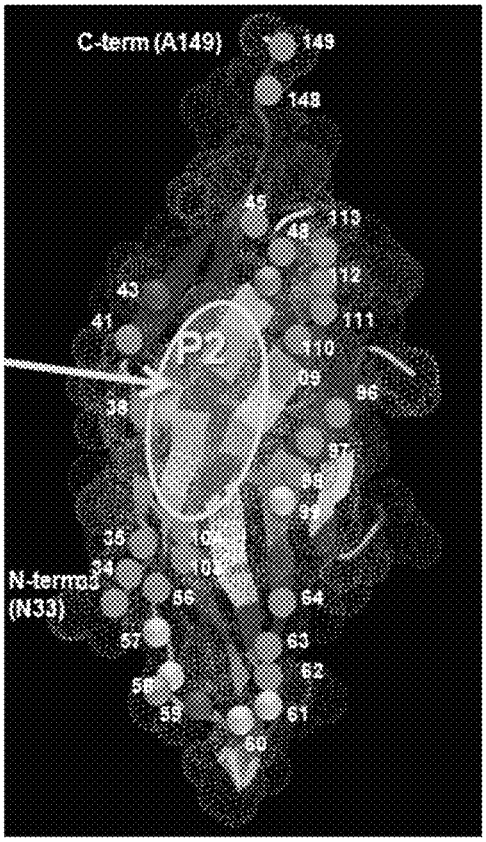
FIG. 17A





Conserved patches on human, rat, monkey, dog and mouse PD-1

FIG. 17B



Variable residues between human and mouse PD-1

Variable residues just between human and dog PD-1

Variable residues between human and monkey PD-1

N-linked glycosylation at residues 49, 58, 74, and 116

FIG. 17C. Alignment of ectodomain amino acid sequences from different species

```
          21                  41                  61
Human     PGWFLDSPDR PW NPPTFSPA LLVVTEGDNA TFTCSFSNTS ESFVLNWYRM SPSNQTDKLA
Monkey    PGWFLESPDR PW NPPTFSPA LLLVTEGDNA TFTCSFSNAS ESFVLNWYRM SPSNQTDKLA
Horse     SVHLLDSPDR PW NRPLFSPA RLMVPEGANA TFTCSFSNTS EHFVLNWYRM SPSNQTDKLA
Dog       PGWLLDSPDR PW SPLTFSPA QLTVQEGENA TFTCSLADIP DSFVLNWYRL SPRNQTDKLA
Mouse     SGWLLEVPNG PW RSLTFYPA WLTVSEGANA TFTCSLSNWS EDLMLNWNRL SPSNQTEKQA
Rat       SGWLLEVLNK PW RPLTFSPT WLTVSEGANA TFTCSFSNWS EDLKLNWYRL SPSNQTEKQA

          81                  101                 121
Human     AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT YLCGAISLAP KAQIKESLRA
Monkey    AFPEDRSQPG RDCRFRVTQL PNGRDFHMSV VRARRNDSGT YLCGAISLAP KAQIKESLRA
Horse     AFPEDSSQPG RSGRFRVTRL PNGRDFHMSV LAARRNDSGI YLCGAISLPP KTQINESPRA
Dog       AFQEDRIEPG RDRRFRVTRL PNGRDFHMSI VAARLNDSGI YLCGAIYLPP NTQINESPRA
Mouse     AFCNGLSQPV QDARFQIIQL PNRHDFHMNI LDTRRNDSGI YLCGAISLHP KAKIEESPGA
Rat       AFCNGYSQPV RDARFQIVQL PNGHDFHMNI LDARRNDSGI YLCGAISLPP KAQIKESPGA

          141                 161
Human     ELRVTERRA E VPTAHPSPSP RPAGQFQTL (SEQ ID NO:207)
Monkey    ELRVTERRA E VPTAHPSPSP RPAGQFQAL (SEQ ID NO:208)
Horse     ELTVTERIP E PPTEHPSPSP SPAGQLQGL (SEQ ID NO:209)
Dog       ELSVTERTL E PPTQSPSPSP RLSGQLQGL (SEQ ID NO:210)
Mouse     ELVVTERIL E TSTRYPSPSP KPEGRFQGM (SEQ ID NO:211)
Rat       ELVVTERIL E TPTRYPRPSP KPEGQFQGL (SEQ ID NO:212)
```

FIG. 18

Competitor Antibody Clones	Affinity (nM)	Binding Class (Luminex Studies)	Functional effect: % CFSE low CD8 T cells	Inhibition of PD-1 / PD-L1 interaction	Binding of labeled mAb in the presence of competitor mAb			
					MK3475	137F2	135C12	134D2
137F2	1.5	1	250%	+++				
139F11	3.1	1	250%	+++				
140G5	1.6	1	205%	+++				
131D11	2.7	1	180%	++				
135C12	1.7	2	195%	NC				
139D6	2.4	2	195%	NC				
136B4	1.4	2	185%	NC				
135D1	6.5	2	187%	NC				
140A1	1.4	3	160%	+++				
135E10	1.5	3	165%	+++				
134D2	4.8	4	205%	++				
136E10	7.1	4	148%	NC				
136F4	8.3	4	108%	NC				
121G1	11.9	4	120%	NC				
136B5	7.7	4	200%	++				
122F10	2.2	4	146%	NC				
BMS-5C4	0.6	1	175%	na				
MK3475	0.5	1	198%	+++				
IgG1	na	na	100%	NC				

0-29%
30-59%
60-79%
80-100%

FIG. 19A

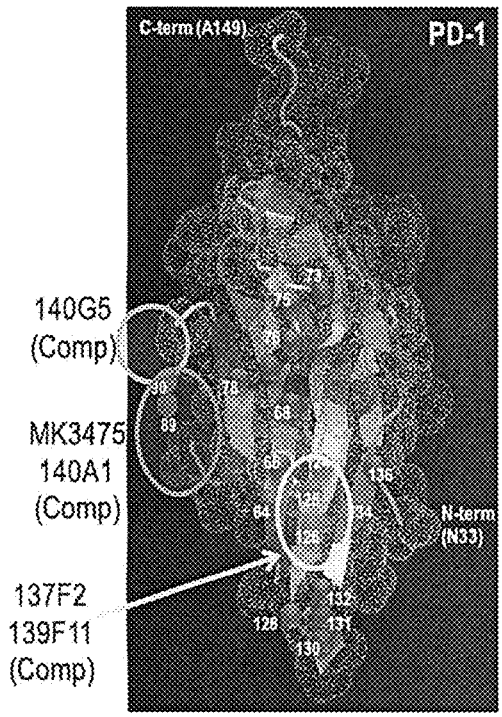
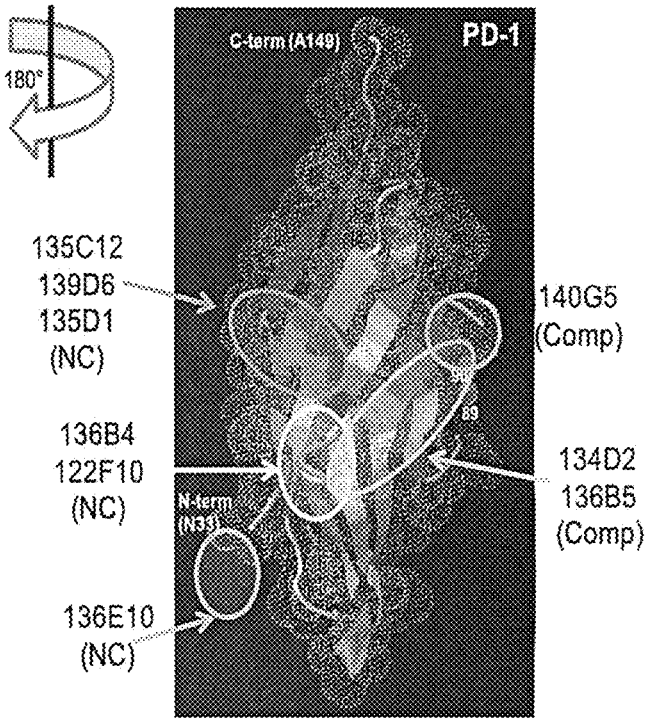


FIG. 19B



Residues at the PD-1/PD-L1 or PD-1/PD-L2 interaction site

Comp Anti-PD-1 antibodies that are competitive with PD-1 /PD-L1 interaction

NC Anti-PD-1 antibodies that are non-competitive with PD-1 /PD-L1 interaction

FIG. 20A

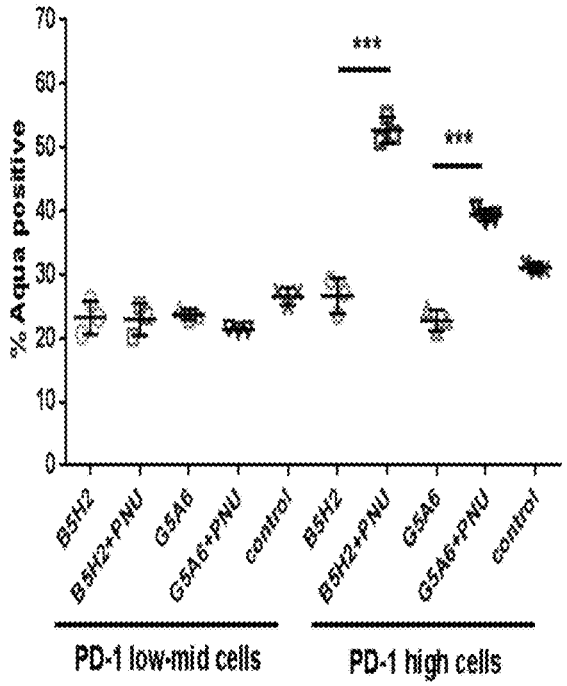


FIG. 20B

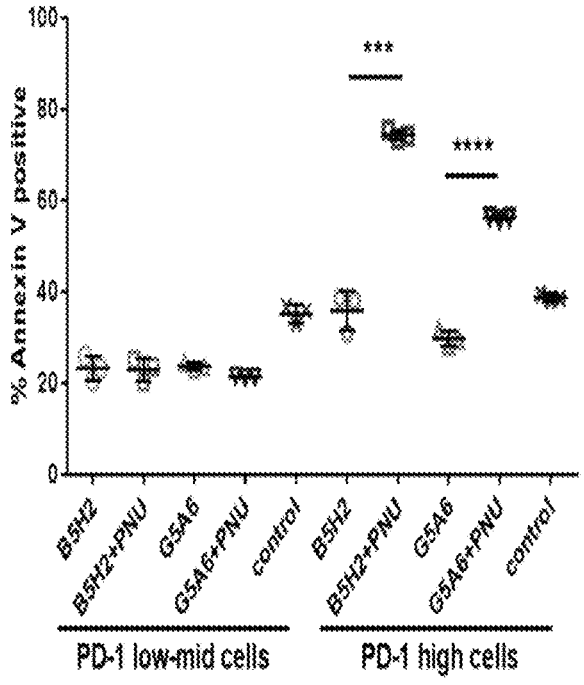


FIG. 21A

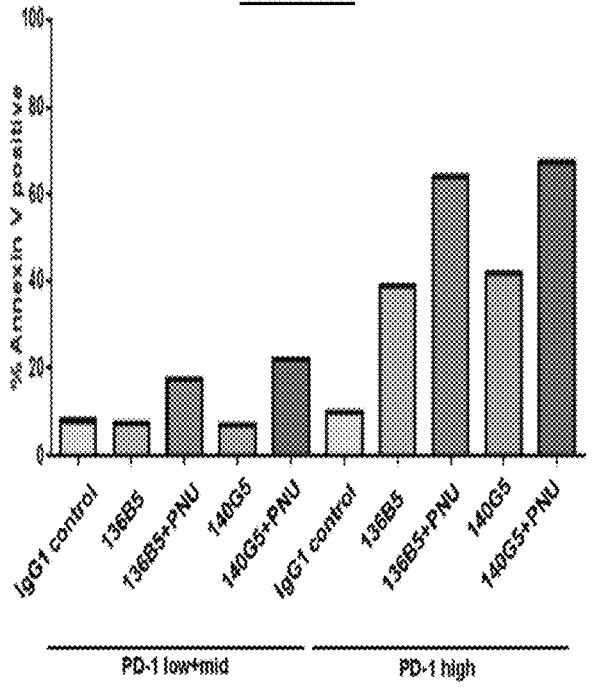


FIG. 21B

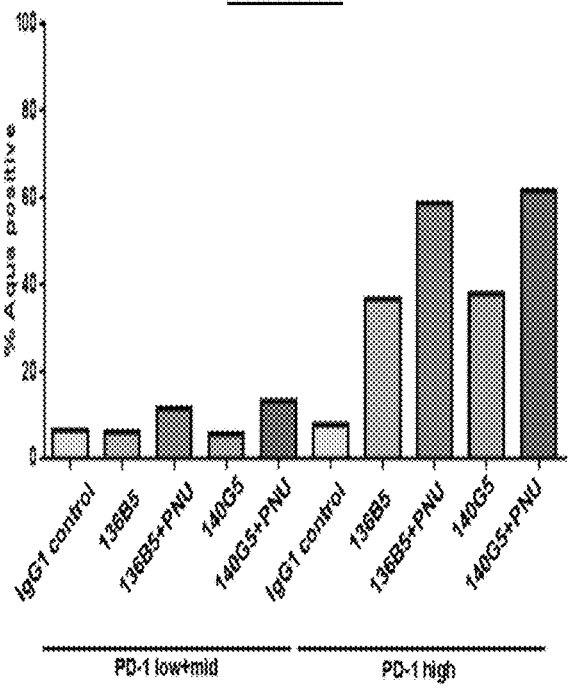
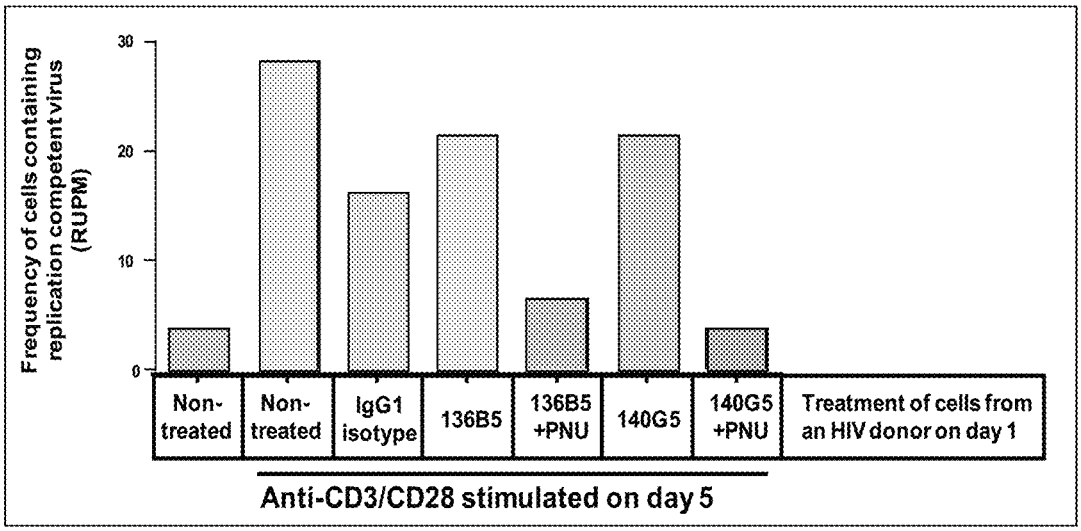


FIG. 22


Frequency of cells containing replication competent virus (RUPM)
30
20
10
0
Non-treated
Non-treated
IgG1 isotype
136B5
136B5 +PNU
140G5
140G5 +PNU
Treatment of cells from an HIV donor on day 1
Anti-CD3/CD28 stimulated on day 5

IMMUNOLOGICAL REAGENTS

RELATED APPLICATIONS

This application is a continuation of U.S. Ser. No. 15/272,707 filed Sep. 22, 2016, now U.S. Pat. No. 9,982,052 B2, which is a continuation of U.S. Ser. No. 15/014,749 filed on Feb. 3, 2016, which claims priority to U.S. Ser. No. 62/286,269 filed Jan. 22, 2016. Each of these applications is hereby incorporated into this disclosure in their entirety.

FIELD OF THE DISCLOSURE

This disclosure relates to binding agents with specificity for programmed cell death 1 (PD-1) (e.g., human PD-1) and to methods for using the same to treat and/or prevent infection (e.g., by human immunodeficiency virus (HIV)), cancer and/or autoimmunity.

BACKGROUND OF THE DISCLOSURE

As we enter the fourth decade of the HIV epidemic, significant advances have been made in the understanding of HIV pathogenesis and in the development of potent and safe antiviral drugs. More than 30 antiviral drugs have been registered and the impact of combination antiretroviral therapy (ART) on both morbidity and mortality has been remarkable. However, despite the long-term suppression of HIV replication achieved in patients with optimal adherence to ART, HIV invariably rebounds after interruption of therapy. Furthermore, successful therapy does not induce or allow restoration/development of virus-specific immune responses capable of controlling HIV replication in the absence of ART. Thus, life-long ART is needed to control HIV replication and associated disease in the large majority of HIV infected subjects.

A population of long-lived central memory CD4 T-cells latently infected with HIV has been identified in the blood as an important component of the HIV cell reservoir and as the primary cause of HIV persistence. The life-span of this latent cell reservoir is estimated to be approximately 70 years in the presence of full HIV suppression with ART. However, recent studies have demonstrated that two populations of CD4 T-cells resident in lymph nodes serve as the primary CD4 T-cell compartment for HIV infection, replication and production. These two CD4 T-cell populations are defined by the expression of PD-1 and CXCR5 and include the PD-1+CXCR5+, i.e. T follicular helper cells (Tfh) and PD-1+CXCR5− CD4 T-cell populations.

A number of mechanisms responsible for the establishment and maintenance of the HIV latent cell reservoir(s) have been proposed. One of the mechanisms is the persistent of minimal virus replication under ART which may replenish the HIV cell reservoir. Therefore, ART is unable to induce full suppression of HIV replication and the "natural" HIV-1 specific immune response under ART is also unable to totally suppress and eliminate ongoing residual virus replication. The failures of ART and of the HIV-specific immune response provide the rationale for investigating alternative interventions to target also the persistent HIV cell reservoir.

A number of immunological interventions have been investigated in the past and currently being further developed with the goal to achieve HIV functional cure, wherein viral replication is suppressed without sustained antiviral therapy (9). Therapeutic vaccine strategies have been the primary intervention strategy investigated but the results

have shown modest efficacy in experimental animal models and patients with the exception of a CMV-based vector HIV vaccine (50% efficacy in the NHP model; 10). Recent studies have generated interesting results on the possibility of using anti-envelope broad neutralizing antibodies (bNabs) as therapeutic agents in HIV infection (11, 12). Furthermore, antagonist PD-1 Abs have been shown to restore T-cell functions in HIV infected patients and the possibility to use these Abs as a therapeutic strategy to augment the potency of HIV-specific T-cell responses has been proposed (13, 14).

It is well established that infiltrating tumor-specific CD8 T-cells are dysfunctional with regard their ability to proliferate and to mediate cytotoxic activity. The large majority of infiltrating tumor-specific CD8 T-cells are in a so-called exhaustion functional state. The primary mechanism responsible for the exhaustion of infiltrating tumor-specific CD8 T-cells is the increased expression of a number of regulatory receptors and particularly PD-1 regulatory receptor. The observation that the blockade of the PD-1/PDL-1/2 (PD-1 ligands) is associated with the recovery of CD8 T-cells from exhaustion has provided the rationale for developing intervention strategies targeting the PD-1 molecule expressed by exhausted CD8 T-cells. Recent studies have shown very promising results with the use of PD-1 antibodies with antagonist activity in patients with advanced cancer-associated disease. Studies have shown substantial rates of response, ranging from 18 to 40%, in patients with advanced melanoma, non-small cell lung carcinoma and renal carcinoma. Anti-PD-1 antibodies in these studies have been used either alone or in combination with an anti-CTL-A4 antibody. After these initial studies, the current studies are being performed in patients with a variety of tumors including also hematological tumors.

There is a need in the art for additional reagents for targeting PD-1 and methods for using the same. This disclosure addresses those needs by providing reagents and methods that may be used to target PD-1 and cells and/or tissues expressing the same.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**. FIG. **1**A. Mouse PD-1. FIG. **1**B. Human PD-1.

FIG. **2**. CFSE assay to evaluate the functional effect of anti-PD1 antibodies on the proliferation of HIV specific CD8 T cells.

FIG. **3**. Concentration response binding of anti-PD-1 antibodies to cell surface PD-1 on activated CD4 T-cells.

FIG. **4**. Antibody classes.

FIG. **5**. Biochemical PD-1/PD-L1 interaction assay to evaluate if antibodies bind PD-1 competitively or non-competitively with PD-L1. FIG. **5**A: Class 1 mAb 137F2; FIG. **5**B: Class 2 mAb 139D6; FIG. **5**C: Class 2 mAb 136B4; FIG. **5**D: Class 1 mAb 137F2; FIG. **5**E: Class 2 mAb 132F7; FIG. **5**F: Class 2 mAb 136B4.

FIG. **6**. Restoration of HIV peptide specific CD8 T-cell proliferation mediated by anti-PD-1 antibodies binding to different epitopes in a functional exhaustion recovery assay. FIG. **6**A: Monoclonal antibodies BMS-5C4, MK3475, 135H12, 122H2, 139D6, 135E10, and 136B5. FIG. **6**B: Monoclonal antibodies MK3475, 135H12, 122H2, 137F2, 135C12, 131D11, and 136B5.

FIG. **7**. Enhanced restoration of HIV peptide specific CD8 T-cell proliferation mediated by select anti-PD-1 antibodies relative to benchmark control antibodies in the functional exhaustion recovery assay.

FIG. **8**. Synergy between a first binding agent that blocks the interaction of PD-1 and PD-L1 with a second binding agent that does not block the interaction of PD-1 and PD-L1.

FIG. **9**. Structural representation of the PD-1 protein ectodomain from residues 33 to 149. Amino acids implicated in the interaction with either PD-L1 or PD-L2 are situated on the structure by the purple circles with the residue number indicated.

FIG. **10**. FIG. **10**A: Amino acid sequence of the ectodomain for human PD-1. Residues that were targeted for amino acid substitutions are indicated for each of the 31 mutations (M1 to M31). Residues in purple text correspond to amino acids that are implicated in the PD-1/PD-L1 interaction and asparagine residues in green are potential sites for N-linked glycosylation. FIG. **10**B: Modified PD-1 polypeptides M1, M2, M4 and M4. FIG. **10**C: Modified PD-1 polypeptides M5, M6, M7, M8, M19 and M10. FIG. **10**D:. Modified PD-1 polypeptides M11, M12, M13, M14, M15 and M16. FIG. **10**E: Modified PD-1 polypeptides M17, M18, M19, M20, M21 and M22. FIG. **10**F: Modified PD-1 polypeptides M23, M24, M25, M26, M27 and M28. FIG. **10**G: Modified PD-1 polypeptides M29, M30 and M31. FIG. **10**H: Human PD-1 amino acid sequence. FIG. **10**I: Monkey PD-1 amino acid sequence.

FIG. **11**. Binding of competitive and non-competitive anti-PD-1 antibodies to modified PD-1 protein expressed at the surface of transiently transfected HeLa cells. FIG. **11**A: PD-1 WT. FIG. **11**B: PD-1 M13. FIG. **11**C: PD-1 M14. FIG. **11**D:. PD-1 M23.

FIG. **12**. Binding of competitive and non-competitive anti-PD-1 antibodies to modified PD-1 protein expressed at the surface of transiently transfected HeLa cells. FIG. **12**A: PD-1 WT. FIG. **12**B: PD-1 M13. FIG. **12**C:. PD-1 M23. FIG. **12**D: PD-1 M4.

FIG. **13**. Binding of competitive and non-competitive anti-PD-1 antibodies to modified PD-1 protein expressed at the surface of transiently transfected HeLa cells. FIG. **13**A: PD-1 WT. FIG. **13**B: PD-1 M31. FIG. **13**C: PD-1 M5. FIG. **13**D: PD-1 M18.

FIG. **14**. Binding of competitive and non-competitive anti-PD-1 antibodies to modified PD-1 protein expressed at the surface of transiently transfected HeLa cells. FIG. **14**A: WT. FIG. **14**B: M1. FIG. **14**C: M9. FIG. **14**D: M13. FIG. **14**E: M17. FIG. **14**F: M18. FIG. **14**G: M23. FIG. **14**H: M28.

FIG. **15**. Combination of two antagonistic anti-PD-1 antibodies binding to different epitopes on PD-1, one competitive and one non-competitive with the PD-1/PD-L1 interaction, results in an enhanced relief of functional exhaustion and increased proliferation of HIV specific CD8 T cells beyond what either antibody alone can achieve.

FIG. **16**. Individual antagonistic anti-PD-1 antibodies and combinations of two antagonistic anti-PD-1 antibodies binding to different epitopes on PD-1 result in enhanced proliferation (FIG. **16**A) and IFNγ production (FIG. **16**B) from PD-1+ memory CD4 T cells in a mixed lymphocyte reaction assay.

FIG. **17**. Structural representation of the P1 (FIG. **17**A) and P2 (FIG. **17**B)) evolutionarily conserved patches of PD-1 along with the alignments of PD-1 ectodomain amino acid sequences from different species (FIG. **17**C).

FIG. **18**. Antibody competitive binding studies for cell surface PD-1 on activated CD4+ T cells.

FIG. **19**. Epitope mapping of antibody binding sites to the structure of PD-1 using a combination of both site directed mutagenesis and antibody competition binding results. FIG. **19**A: First view. FIG. **19**B: 180° View.

FIG. **20**. Selective increase in apoptosis (Annexing V staining) or cell death (Aqua staining) in PD-1 high CD4 T cells from a viremic HIV infected donor upon treatment with an anti-PD-1 ADC as opposed to either anti-PD-1 antibodies alone or an IgG control antibody. FIG. **20**A: % Aqua positive. FIG. **20**B: % Annexin positive.

FIG. **21**. Cytotoxicity of anti-PD1 antibody drug conjugates. FIG. **21**A: Annexin V positive. FIG. **21**B: % Aqua positive.

FIG. **22**. Evaluation of the anti-PD-1 antibody drug conjugate (ADC) mediated killing of PD-1 positive infected CD4 T cells from a chronically infected HIV donor. Following 5 days of antibody treatment, cells were used in a quantitative viral outgrown assay to monitor the number of infectious cells in the different treated samples.

SUMMARY OF THE DISCLOSURE

This disclosure relates to binding agents with specificity for programmed cell death 1 (PD-1) (e.g., human PD-1) and to methods for using the same such as to treat, prevent and/or ameliorate infection (e.g., by human immunodeficiency virus (HIV)), cancer and/or an autoimmune condition. Functional assays for identifying binding agents that interact with PD-1 are also provided. Combinations of binding agents, such as a first binding agent that blocks the interaction of PD-1 and PD-L1 with a second binding agent that does not block the interaction of PD-1 and PD-L1, are also provided that act synergistically to rescue T cells from exhaustion.

DETAILED DESCRIPTION

This disclosure relates to binding agents that bind programmed cell death (PD-1) protein (e.g., SEQ ID NO:1, FIG. 1A, FIG. 1B of U.S. Pat. No. 5,698,520 (Honjo, et al.) which is hereby incorporated by reference in its entirety) (e.g., human PD-1) on the surface of cells in vitro and/or in vivo. The binding agents may also bind isolated PD-1 polypeptide (e.g., human PD-1) and/or fragments and/or derivatives thereof, typically in vitro. Also provided are methods for using such binding agents to diagnose, treat, prevent and/or ameliorate one or more diseases associated with the existence of cells expressing PD-1. For instance, the binding agents may be antibodies (e.g., monoclonal antibodies) that may react with and/or bind to the epitopes of PD-1. The "binding agents" described herein may include, for example, an agonist or an antagonist of PD-1. An agonist binding agent is one that is not typically capable of restoring T-cell function and/or expression of PD-1. An agonist PD-1 binding agent may be useful for treating autoimmune diseases and others in which PD-1 expressing cells are involved in disease progression. In contrast, an antagonist binding agent is one capable for restoring T-cell function and/or expression of PD-1. For instance, a PD-1 antagonist binding agent may be capable of restoring the function of PD-1 expressing T-cells from functional exhaustion as is known to occur in HIV infection and in a variety of tumors. Restoration of T cell function may be determined by, for instance, measuring proliferation, cytokine production, cytotoxic activity or other characteristics of such cells. Another use for the binding agents described herein is the selective targeting and elimination of HIV-infected $CD4^+$ T-cell populations containing replication competent HIV (e.g., in a latent and/or replication state). Such PD-1 expressing cells expressing PD-1 are known to serve as a major cell reservoir for replication competent HIV. A potential mechanism for the elimination of these $CD4^+$ T-cell populations is anti-

body-dependent cellular cytotoxicity (ADCC) using the binding agents described herein (e.g., mono- and/or bi-specific PD-1 antibodies). In some embodiments, one or more PD-1 antagonistic binding agents having, for instance, different specificities (e.g., recognizing different epitopes) may be combined to induce rescue of antigen-specific $CD8^+$ T-cells from functional exhaustion caused by PD-1 expression in those cells (e.g., restoring or improving proliferation, cytokine production and/or cytotoxic activity). In some embodiments, the binding agents described herein may also provide for the selective elimination and/or suppression of PD-1 expressing cells. In some embodiments, the PD-1 agonist binding agents described herein may be used to supress and/or eliminate PD-1 expressing cells to treat, for instance, infectious diseases (e.g., HIV), cancer, and/or, especially, autoimmune conditions. Other embodiments, uses and the like are described below.

The binding agents may be antibodies such as monoclonal antibodies that may comprise, for instance, any one or more of the amino acid sequences shown in Table 1 (and/or one or more fragments and/or derivatives thereof). This disclosure also provides for the use of such monoclonal antibodies to isolate, identify, and/or target cells expressing PD-1. In certain embodiments, these monoclonal antibodies may be reactive against PD-1 expressed on the surface of cells. The term "antibody" or "antibodies" may refer to whole or fragmented antibodies in unpurified or partially purified form (e.g., hybridoma supernatant, ascites, polyclonal antisera) or in purified form. The antibodies may be of any suitable origin or form including, for example, murine (e.g., produced by murine hybridoma cells), or expressed as humanized antibodies, chimeric antibodies, human antibodies, and the like. For instance, antibodies may be wholly or partially derived from human (e.g., IgG (IgG1, IgG2, IgG2a, Ig2b, IgG3, IgG4), IgM, IgA (IgA1 and IgA2), IgD, and IgE), canine (e.g., IgGA, IgGB, IgGC, IgGD), chicken (e.g., IgA, IgD, IgE, IgG, IgM, IgY), goat (e.g., IgG), mouse (e.g., IgG, IgD, IgE, IgG, IgM), and/or pig (e.g., IgG, IgD, IgE, IgG, IgM), rat (e.g., IgG, IgD, IgE, IgG, IgM) antibodies, for instance. Methods of preparing, utilizing and storing various types of antibodies are well-known to those of skill in the art and would be suitable in practicing the present invention (see, for example, Harlow, et al. *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988; Harlow, et al. *Using Antibodies: A Laboratory Manual*, Portable Protocol No. 1, 1998; Kohler and Milstein, Nature, 256:495 (1975)); Jones et al. Nature, 321:522-525 (1986); Riechmann et al. Nature, 332:323-329 (1988); Presta (Curr. Op. Struct. Biol., 2:593-596 (1992); Verhoeyen et al. (Science, 239:1534-1536 (1988); Hoogenboom et al., J. Mol. Biol., 227:381 (1991); Marks et al., J. Mol. Biol., 222:581 (1991); Cole et al., Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, p. 77 (1985); Boerner et al., J. Immunol., 147(1):86-95 (1991); Marks et al., Bio/Technology 10, 779-783 (1992); Lonberg et al., Nature 368 856-859 (1994); Morrison, Nature 368 812-13 (1994); Fishwild et al., Nature Biotechnology 14, 845-51 (1996); Neuberger, Nature Biotechnology 14, 826 (1996); Lonberg and Huszar, Intern. Rev. Immunol. 13 65-93 (1995); as well as U.S. Pat. Nos. 4,816,567; 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; and, 5,661,016). In certain applications, the antibodies may be contained within hybridoma supernatant or ascites and utilized either directly as such or following concentration using standard techniques. In other applications, the antibodies may be further purified using, for example, salt fractionation and ion exchange chromatography, or affinity chromatography using Protein A, Protein G, Protein A/G, and/or Protein L ligands covalently coupled to a solid support such as agarose beads, or combinations of these techniques. The antibodies may be stored in any suitable format, including as a frozen preparation (e.g., −20° C. or −70° C.), in lyophilized form, or under normal refrigeration conditions (e.g., 4° C.). When stored in liquid form, for instance, it is preferred that a suitable buffer such as Tris-buffered saline (TBS) or phosphate buffered saline (PBS) is utilized. In some embodiments, the binding agent may be prepared as an injectable preparation, such as in suspension in a non-toxic parenterally acceptable diluent or solvent. Suitable vehicles and solvents that may be utilized include water, Ringer's solution, and isotonic sodium chloride solution, TBS and/or PBS, among others. Such preparations may be suitable for use in vitro or in vivo may be prepared as is known in the art and the exact preparation may depend on the particular application.

However, the binding agents described are not in any way limited to antibodies. For example, the binding agent may be any compound exhibiting similar binding properties as another (e.g., a mimetic). For example, an exemplary binding agent may be one that binds PD-1 and/or can compete with binding agent having specificity therefor (e.g., a monoclonal antibody). In some embodiments, the mimetic may exhibit substantially the same affinity in binding assays as the binding agent (e.g., monoclonal antibody) to which it is being compared. The affinity a particular binding agent may be measured by any suitable assay including but not limited to FACS staining of endogenous cell surface PD-1 on activated CD4 T cells as described in the Examples. One binding agent may be said to have "substantially the same affinity" as another where the measurements (e.g., nm) are within about any of 1-20, 1-5, 5-10, 10-15, or 15-20 percent of one another. Exemplary mimetics may include, for example, organic compounds that specifically bind PD-1, or an affibody (Nygren, et al. FEBS J. 275 (11): 2668-76 (2008)), affilin (Ebersbach, et al. J. Mol. Biol. 372 (1): 172-85 (2007)), affitin (Krehenbrink, et al. J. Mol. Biol. 383 (5): 1058-68 (2008)), anticalin (Skerra, A. FEBS J. 275 (11): 2677-83 (2008)), avimer (Silverman, et al. Nat. Biotechnol. 23 (12): 1556-61 (2005)), DARPin (Stumpp, et al. Drug Discov. Today 13 (15-16): 695-701 (2008)), Fynomer (Grabulovski, et al. J. Biol. Chem. 282 (5): 3196-3204 (2007)), Kunitz domain peptide (Nixon, et al. Curr. Opin. Drug Discov. Devel. 9 (2): 261-8 (2006)), and/or a monobody (Koide, et al. Methods Mol. Biol. 352: 95-109 (2007)). Other mimetics may include, for example, a derivative of an antibody (of, for example, the monoclonal antibody 1E4, 1G10, and/or 1G1) such as, for example, an F_{ab}, F_{ab2}, Fab' single chain antibody, F_v, single domain antibody, monospecific antibody, bi-specific antibody, tri-specific antibody, multi-valent antibody, chimeric antibody, canine-human chimeric antibody, canine-mouse chimeric antibody, antibody comprising a canine Fc, humanized antibody, human antibody, caninized, CDR-grafted antibody, shark antibody, nanobody, canelid antibody, microbody, and/or intrabody, or derivative thereof. Other binding agents are also provided herein as would be understood by one of ordinary skill in the art.

Any method known to those of ordinary skill in the art may be used to generate binding agents having specificity for (e.g., binding to) PD-1. For instance, to generate and isolate monoclonal antibodies an animal such as a mouse may be administered (e.g., immunized) with one or more PD-1 proteins (e.g., PD-1 Fc fusion protein and/or PD-1 His tag protein). Animals exhibiting serum reactivity to PD-1 expressed on activated human T lymphocytes (as deter-

mined by, for instance, flow cytometry and/or microscopy) may then be selected for generation of anti-PD-1 hybridoma cell lines. This may be repeated for multiple rounds. For instance, the primary criteria for the first round of binding agent selection may be include but are not limited to: i) level of staining of PD-1 on activated human T lymphocytes by flow cytometry; (ii) diversity of CDR VH and VL sequences as compared to those of the existing anti-PD-1 antibodies; and, (iii) epitope mapping performed by competitive binding studies with PD-1 conjugated Luminex beads pre-coupled with PD-L1 or one of several commercially available anti-PD-1 antibodies binding to different epitopes on PD-1. An exemplary first or second round of selection may also include, for instance, affinity binding (not a primary criteria since it may not correlate with the stimulatory potential of anti-PD-1 antibodies); and/or, functional characterization to identify the binding agent as an agonist or an antagonist.

As described in Example 1 herein, for instance, the Exhaustion Functional Recovery Assay (EFRA) may be used. In this assay, test binding agents may be assayed for the ability to rescue immune cells such as T cells from exhaustion. This may be determined by measuring the ability of a binding agent to restore proliferation to such cells in the presence of an antigen, such as a test peptide derived from a virus such as human immunodeficiency virus (HIV). Proliferation is measured in a CFSE assay in comparison to a control, such as the test peptide alone or a positive control anti-PD-1 antibody such as MK-3475 (pembrolizumab). In some embodiments, a binding agent is determined to restore proliferation where the comparison shows a significant difference (such as a P value of <0.001) compared to either a peptide alone control or peptide with an isotype control mouse IgG1 antibody. This assay may be used to identify binding agents (such as antibodies) that compete with other binding agents for binding to PD-1 (such as PD-L1 or PD-L2) and/or lead to the functional restoration of immune cells. Example 1 also describes two methods of epitope mapping the antibodies listed in Table 2 using Luminex-based assays. In one biochemical assay, a PD-1 Fc fusion protein is bound to beads and competitive binding studies are performed between the anti-PD-1 antibodies described in Table 2 and one of two different commercially available anti-PD-1 antibodies. Example 1 describes four classes of monoclonal antibodies binding to distinct epitopes on PD-1 that were: class 1 (competitive with a first monoclonal antibody that blocks the interaction of PD-1 with PD-L1), class 2 (competitive with a second monoclonal antibody that binds PD-1 but does not block the interaction of PD-1 with PD-L1), class 3 (competitive with both the first and second monoclonal antibodies), and class 4 (non-competitive with either the first or second antibodies). In a seperate assay, competition for binding to a recombinant PD-1 protein was evaluated for the anti-PD-1 antibodies listed in Table 2 and a biotinylated PD-L1 recombinant protein. Antibodies that induced proliferation in the EFRA were identified from all four binding classes that are proposed of binding to different epitopes on PD-1. Likewise, the EFRA allowed for the identification of anti-PD-1 antibodies that were either competitive, partially competitive or non-competitive with the PD-1/PD-L1 interaction and specifically restored proliferative function to HIV specific $CD8^+$ T-cell.

Combinations of binding agents may also be identified. In some embodiments, the combinations may be identified to provide statistically significant differences from results obtained using only one or more of the binding agents and not others. In some embodiments, combinations exhibiting synergistic ability to restore immune cell function may be identified. In some embodiments, the combination may comprise a first binding agent that blocks the interaction of PD-1 and PD-L1 with a second binding agent that does not block the interaction of PD-1 and PD-L1. The first and second binding agents may be different entities such as two or more different monoclonal antibodies or derivatives thereof, or may be found on the same entity such as a bi-functional antibody (a single antibody or derivative thereof comprising multiple binding specificities). For instance, an exemplary bi-functional antibody may comprise a first binding region that blocks the interaction of PD-1 and PD-L1 and a second binding region that does not block the interaction of PD-1 and PD-L1. Also contemplated are combinations that provide multiple types of each binding agent. For instance, the combination may comprise multiple types of binding agents that block the interaction of PD-1 and PD-L1 with one or more that does not block the interaction of PD-1 and PD-L1. In some embodiments, the combination may comprise one or more of binding agents that block the interaction of PD-1 and PD-L1 with multiple binding agents that do not block the interaction of PD-1 and PD-L1. In some embodiments, the combination may comprise multiple binding agents that block the interaction of PD-1 and PD-L1 with multiple binding agents that do not block the interaction of PD-1 and PD-L1. Such combinations as described herein may also be combined with one or more other agents that may effect immune cell function such as antibodies against CTLA-4 and the like. One of ordinary skill in the art would recognize that many such combinations may be suitable for use as described herein.

Where the binding agent is an antibody, it may be identified with reference to the nucleotide and/or amino acid sequence corresponding to the variability and/or complementarity determining regions ("CDRs") thereof. The variable region/CDR sequences may be used in combination with one or more other variable region/CDR amino acid sequences. The variable region/CDR amino acid sequences may alternatively and/or also be adjoined to one or more types of constant region polypeptides of an antibody molecule. For instance, the CDR amino acid sequences shown in Tables 1A and 1B may be adjoined to or associated with the constant regions of any antibody molecule of the same or a different species (e.g., human, goat, rat, sheep, chicken) and/or antibody subtype of that from which the CDR amino acid sequence was derived. For instance, an exemplary binding agent may be, or may be derived from, or may be related to the monoclonal antibody produced by the hybridomas listed in, and/or may have about the same affinity and/or proliferation effect, and/or exhibit the same binding class shown in Table 2, 5, 6 or 7 and/or may have any one or more of the amino acid sequences of SEQ ID NOS. 1-138 and/or as shown in Tables 1A and 1B. The binding agent may comprise an antibody heavy and/or a light chain that each comprises one or more constant and/or variable regions. The variable regions typically comprise one or more CDRs that may determine the binding specificity of the antibody. The monoclonal antibodies may also be identified by analysis of the amino acid sequences of (e.g., which may be encoded by such nucleotide sequences) such variable regions. For instance, exemplary amino acid sequences of the heavy chain CDRs of binding agents that bind PD-1 may include any one or more of comprising at least one amino acid sequence selected from the group consisting of SEQ ID NOS. 1-138, and/or any other shown in Tables 1A and/or 1B. Any of the amino acid sequences described herein, and/or any fragments and/or derivatives thereof may also be combined with any other variable region and/or CDR in any

order and/or combination to form hybrid and/or fusion binding agents and/or inserted into other heavy and/or light chain variable regions using standard techniques. Exemplary combinations of CDRs (e.g., combination of heavy and/or light chain CDR1, CDR2 and CDR3 amino acid sequences) that may be found in a PD-1 (e.g., human PD-1) binding agent of this disclosure may include, for instance, the embodiments shown in Tables 1A and/or 1B.

TABLE 1A

	Heavy chain: Amino acids sequence		
Clone	CD121	CDR2	CDR3
122F10	DDFLH (SEQ ID NO: 1)	RIDPANGESRYAPKFQD (SEQ ID NO: 24)	TDYRGYYYAMDY (SEQ ID NO: 47)
139D6	NYYIH (SEQ ID NO: 2)	SIYPNYGDTNYNQKVKD (SEQ ID NO: 25)	GYSYAMDY (SEQ ID NO: 48)
135D1	NYYIH (SEQ ID NO: 3)	SIYPNYGETNYNQEFKG (SEQ ID NO: 26)	GYSYAMDY (SEQ ID NO: 49)
134D2	SNWMH (SEQ ID NO: 4)	AVNPGNSDTTYNQKFKG (SEQ ID NO: 27)	GRSYDGSFDY (SEQ ID NO: 50)
121G1	RYWMH (SEQ ID NO: 5)	NIDPSDSTTHYNPKFRD (SEQ ID NO: 28)	DLDDFYVGSHEDFDY (SEQ ID NO: 51)
136B5	SNWMH (SEQ ID NO: 6)	AVYPGNSDTTYNQNFKG (SEQ ID NO: 29)	GRSYDGSFDY (SEQ ID NO: 52)
127C2	NSYIH (SEQ ID NO: 7)	WISPGDGSTNYNEKFKG (SEQ ID NO: 30)	EEYDYDNY (SEQ ID NO: 53)
137F2	NYWIG (SEQ ID NO: 8)	DIYPGGGYTNYNEKFKG (SEQ ID NO: 31)	GYDFVLDR (SEQ ID NO: 54)
138H5	SYAMS (SEQ ID NO: 9)	TISGGGADTYYLDNVKG (SEQ ID NO: 32)	QRGENLFAH (SEQ ID NO: 55)
140A1	SDYAWN (SEQ ID NO: 10)	YINYSGYTNYNPFLKS (SEQ ID NO: 33)	YGGSYPWNFDV (SEQ ID NO: 56)
135H12	SYWIN (SEQ ID NO: 11)	NIYPGSSSIDYNEKFKS (SEQ ID NO: 34)	GLYWYFDV (SEQ ID NO: 57)
131D11	SSYIH (SEQ ID NO: 12)	WIFPGDGKTNYNEKFRD (SEQ ID NO: 35)	NDFDRGVY (SEQ ID NO: 58)
132F7	NHGMS (SEQ ID NO: 13)	SINTGGYSTYYPDNVKG (SEQ ID NO: 36)	DDYNWFAY (SEQ ID NO: 59)
126E4	NYWIG (SEQ ID NO: 14)	DIYPGSEYENYNEKFKG (SEQ ID NO: 37)	GYDFVLDH (SEQ ID NO: 60)
135G1	DSYIH (SEQ ID NO: 15)	RIDPAHGNVIYASKFRD (SEQ ID NO: 38)	IYYDYGEGDF (SEQ ID NO: 61)
136E10	DTYIH (SEQ ID NO: 16)	RIDLANDDILYASKFQG (SEQ ID NO: 39)	IYYDYGEGDY (SEQ ID NO: 62)
135C12	NFYIH (SEQ ID NO: 17)	SIYPNYGDTAYNQKFKD (SEQ ID NO: 40)	GYSYAMDY (SEQ ID NO: 63)
136F4	DSYIH (SEQ ID NO: 18)	RIDPARDNIIYASKFRD (SEQ ID NO: 41)	IYYDYGEGDY (SEQ ID NO: 64)
136B4	DDFLH (SEQ ID NO: 19)	RIDPANGESRYAPQFQD (SEQ ID NO: 42)	TDYRGYYYAMDY (SEQ ID NO: 65)
135E10	SYFMS (SEQ ID NO: 20)	GISTGGADTYYADSMKG (SEQ ID NO: 43)	LSHYYDGIPLDC (SEQ ID NO: 66)
140G5	NHGMS (SEQ ID NO: 21)	SISGGGDNTYYPDNLKG (SEQ ID NO: 44)	VRQLGLHRAAMDY (SEQ ID NO: 67)
122H2	NYWIG (SEQ ID NO: 22)	DIYPGGDHKNYNEKFKD (SEQ ID NO: 45)	GFDFVLDY (SEQ ID NO: 68)
139F11	SFAMS (SEQ ID NO: 23)	TITGGGVNTYYPDTVKG (SEQ ID NO: 46)	QAIYDGHYVLDY (SEQ ID NO: 69)

TABLE 1B

	Light chain: Amino acids sequence		
Clone	CDR1	CDR2	CDR3
122F10	KSSQSVLYSSNQKNYLA (SEQ ID NO: 70)	WASTRES (SEQ ID NO: 93)	HQYLSSYT (SEQ ID NO: 116)
139D6	SASQGISDGLN (SEQ ID NO: 71)	HTSTLHS (SEQ ID NO: 94)	QQYSKFPLT (SEQ ID NO: 117)
135D1	SASQGISNGLN (SEQ ID NO: 72)	HTSTLHS (SEQ ID NO: 95)	QQYSKFPLT (SEQ ID NO: 118)
134D2	KASQDINKYIA (SEQ ID NO: 73)	YTSTLRP (SEQ ID NO: 96)	LQYDNLWT (SEQ ID NO: 119)
121G1	RSSQSIVYSNGNTYLE (SEQ ID NO: 74)	KVSHRFS (SEQ ID NO: 97)	FQGSHVPYT (SEQ ID NO: 120)
136B5	KASQDINKYMA (SEQ ID NO: 75)	YTSTLRP (SEQ ID NO: 98)	LQYDNLWT (SEQ ID NO: 121)
127C2	KASQNVGTNVG (SEQ ID NO: 76)	SASYRYN (SEQ ID NO: 99)	QQYNTYPWT (SEQ ID NO: 122)
137F2	KSSQSLFNSETQKNYLA (SEQ ID NO: 77)	WASTRES (SEQ ID NO: 100)	KQSYTLRT (SEQ ID NO: 123)
138H5	LASQTIGTWLA (SEQ ID NO: 78)	AATSLAD (SEQ ID NO: 101)	QQLYSTPWT (SEQ ID NO: 124)
140A1	RSSQTIVHNNGDTYLE (SEQ ID NO: 79)	KISNRFF (SEQ ID NO: 102)	FQGSHVPYT (SEQ ID NO: 125)
135H12	KSSQSLENSGTRKNYLA (SEQ ID NO: 80)	WASTRDS (SEQ ID NO: 103)	KQSYNLYT (SEQ ID NO: 126)
131D11	KASQNVDTNVA (SEQ ID NO: 81)	SASYRYN (SEQ ID NO: 104)	QQYNNYPYT (SEQ ID NO: 127)
132F7	KSSQSLLNSGNQKNYLT (SEQ ID NO: 82)	WASTRES (SEQ ID NO: 105)	QSDYSYPLT (SEQ ID NO: 128)
126E4	KSSQSLENSGTRKSYLA (SEQ ID NO: 83)	WASTRET (SEQ ID NO: 106)	MQSYNLRT (SEQ ID NO: 129)
135G1	HASQNINVWLS (SEQ ID NO: 84)	KASNLHT (SEQ ID NO: 107)	QQGQSWPLT (SEQ ID NO: 130)
136E10	HASQNINVWLS (SEQ ID NO: 85)	KASNLHT (SEQ ID NO: 108)	QQGQSYPLT (SEQ ID NO: 131)
135C12	SASQGISGDLN (SEQ ID NO: 86)	HTSSLHS (SEQ ID NO: 109)	QYYSKDLLT (SEQ ID NO: 132)
136F4	HASQNINVWLS (SEQ ID NO: 87)	KASNLHT (SEQ ID NO: 110)	QQGQSWPLT (SEQ ID NO: 133)
136B4	KSSQSVLYSSNQKNYLA (SEQ ID NO: 88)	WASTRES (SEQ ID NO: 111)	HQYLSSYT (SEQ ID NO: 134)
135E10	RASESVDNSGVSFLT (SEQ ID NO: 89)	AASNQGS (SEQ ID NO: 112)	QQTKEVPWT (SEQ ID NO: 135)
140G5	KASQSVSDDVS (SEQ ID NO: 90)	SAFFRYP (SEQ ID NO: 113)	QQDYSSPLT (SEQ ID NO: 136)
122H2	KSSQSLENSGTRKNYLA (SEQ ID NO: 91)	WASTRES (SEQ ID NO: 114)	MQSFNLRT (SEQ ID NO: 137)
139F11	RTSGNIHNYLA (SEQ ID NO: 92)	NVKTLTD (SEQ ID NO: 115)	QQFWSIPWT (SEQ ID NO: 138)

In addition, any of SEQ ID NOS. 1-69 may be combined with any one or more of SEQ ID NOS. 70-138 into a binding agent. In preferred embodiments, the heavy chain CDRs of each clone are combined with their respective light chain CDRs into a binding agent. In some embodiments, the binding agent may comprise the heavy chain CDRs and light chain CDRs shown below:

122F10 (SEQ ID NOS. 1, 24, 47, 70, 93, and 116);

139D6 (SEQ ID NOS. 2, 25, 48, 71, 94, and 117);

135D1 (SEQ ID NOS. 3, 26, 49, 72, 95, and 118);

134D2 (SEQ ID NOS. 4, 27, 50, 73, 96, and 119);

121G1 (SEQ ID NOS. 5, 28, 51, 74, 97, and 120);

136B5 (SEQ ID NOS. 6, 29, 52, 75, 98, and 121);

127C2 (SEQ ID NOS. 7, 30, 53, 76, 99, and 122);

137F2 (SEQ ID NOS. 8, 31, 54, 77, 100, and 123);

138H5 (SEQ ID NOS. 9, 32, 55, 78, 101, and 124);

140A1 (SEQ ID NOS. 10, 33, 56, 79, 102, and 125);

135H12 (SEQ ID NOS. 11, 34, 57, 80, 103, and 126);

131D11 (SEQ ID NOS. 12, 35, 58, 81, 104, and 127);

132F7 (SEQ ID NOS. 13, 36, 59, 82, 105, and 128);

126E4 (SEQ ID NOS. 14, 37, 60, 83, 106, and 129);

135G1 (SEQ ID NOS. 15, 38, 61, 84, 107, and 130);

136E10 (SEQ ID NOS. 16, 39, 62, 85, 108, and 131);

135C12 (SEQ ID NOS. 17, 40, 63, 86, 109, and 132);

136F4 (SEQ ID NOS. 18, 41, 64, 87, 110, and 133);

136B4 (SEQ ID NOS. 19, 42, 65, 88, 111, and 134);

135E10 (SEQ ID NOS. 20, 43, 66, 89, 112, and 135);

140G5 (SEQ ID NOS. 21, 44, 67, 90, 113, and 136);

122H2 (SEQ ID NOS. 22, 45, 68, 91, 114, and 137); or

139F11 (SEQ ID NOS. 23, 46, 69, 92, 115, and 138).

Other combinations may also be useful as may ascertained by one of ordinary skill in the art.

Binding agents comprising the CDRs of Tables 1A and/or 1B, or those of the immediately preceding paragraph, may also exhibit the following characteristics:

TABLE 2

Clone	Affinity* (nM)	Binding Class**	Antibody competition with the PD-1/PD-L1 interaction***	EFRA % relative to peptide stimulation alone‡
122F10	2.2	4	Non-competitive	146%
139D6	2.4	2	Partial competition	195%
135D1	6.5	2	Partial competition	187%
134D2	4.8	4	Competitive	205%
121G1	11.9	4	Non-competitive	120%
136B5	7.7	4	Competitive	200%
127C2	1.0	2	Non-competitive	100%
137F2	1.5	1	Competitive	250%
138H5	1.6	3	Competitive	210%
140A1	1.4	3	Competitive	160%
135H12	1.9	1	Competitive	190%
131D11	2.7	1	Competitive	180%
132F7	100	2	Non-competitive	210%
126E4	0.5	4	Competitive	130%
135G1	32	4	NA	138%
136E10	7.1	4	Non-competitive	148%
135C12	1.7	2	Partial competition	195%
136F4	8.3	4	Non-competitive	108%
136B4	1.4	2	Non-competitive	185%
135E10	1.5	3	Competitive	165%
140G5	1.6	1	Competitive	205%
122H2	4.3	1	Competitive	200%
139F11	3.1	1	Competitive	250%

*Binding affinity for the antibodies listed in Table 1 was evaluated by FACS staining of endogenous cell surface PD-1 on activated CD4 T cells.

**Binding class was determined by Luminex assay competitive binding studies. Binding class 1 mAb clones are competitive with the EH12.2H7 clone commercial antibody, class 2 mAb clones are competitive with the J116 clone commercial antibody, class 3 mAb clones are competitive with both EH12.2H7 and J116 antibodies and class 4 mAb clones bind in the presence of both EH12.2H7 and J116 antibodies.

***Antibody competition with the PD-1/PD-L1 interaction was determined in a second Luminex binding assay. In this assays, PD-1 Fc fusion protein coated beads were incubated in the absence or presence of an anti-PD-1 antibody from Table 2 at a concentration of 20 nM. A fixed concentration of 1.25 nM biotinylated PD-L1, approximately equivalent to the IC_{50} of the PD-1/PD-L1 interaction, was then incubated with the PD-1/antibody complex and PD-L1 binding was detected by fluorescence with phycoerythrin labeled streptavidin. Based on PD-L1 binding to the PD-1/antibody complex, antibodies were defined as being competitive, partially competitive or non-competitive with the PD-1/PD-L1 interaction.

‡Proliferative effect is evaluated using a CFSE assay (an embodiment of the Exhaustion Functional Recovery Assay, "EFRA"). PBMCs isolated from a chronically infected HIV subject were stimulated with an HIV specific peptide in the presence and absence of an anti-PD-1 antibody. Following a 6 day incubation, proliferation of HIV specific CD8 T cells was evaluated in the anti-PD-1 treated samples relative to the peptide alone control.

NA = not available

As explained in the Examples section, epitope mapping studies revealed at least two conserved patches (comprising linear and/or conformational epitopes) on PD-1 to which the binding agents described herein may bind, designated "P1" and "P2" (see, e.g., FIGS. **17***a* and **17***b*). The P1 patch is evolutionarily conserved and corresponds to the central region of PD-1 involved in the interaction between PD-1 and the PD-L1/PD-L2 ligands, and corresponds with purple circles in FIG. **9** and FIG. **19***a*. The second "patch" P2 is also evolutionarily conserved and occupies a similar surface area but different amino acid sequences (FIG. **17***b*) as the P1 patch. P2 has no previously identified structural or functional role on PD-1. PD-1 binding agents described herein, such as anti-PD-1 antibodies comprising the amino acid sequences of 135C12 (SEQ ID NOS. 17, 40, 63, 86, 109, and 132), 139D6 (SEQ ID NOS. 2, 25, 48, 71, 94, and 117), 135D1 (SEQ ID NOS. 3, 26, 49, 72, 95, and 118), and 136B4 (SEQ ID NOS. 19, 42, 65, 88, 111, and 134), bind epitopes overlapping the P2 patch, thereby providing direct evidence for the functional importance of this newly identified functional region of PD-1. The Examples section describes epitope mapping studies that were carried out using modified PD-1 polypeptides shown in FIG. **10** and SEQ ID NOS. 139-168 and No. 206. These studies revealed that the non-competitive antibodies with the greatest "functional potency" or "antagonistic activity" bind to a "patch" of PD-1 that overlaps with the region of the M4 amino acid substitutions (serine 38 to alanine, proline 39 to alanine and leucine 41 to alanine (FIG. **10**; SEQ ID NO. 142)), and/or the region of the M17 amino acid substitutions (asparagine 102 to alanine and arginine 104 to leucine (FIG. **10**; SEQ ID NO. 155)), and/or the region of the M18 amino acid substitutions (aspartate 105 to alanine (FIG. **10**; SEQ ID NO. 156), and/or the region of the M31 amino acid substitutions (leucine 41 to alanine and valine 43 to leucine (FIG. **10**; SEQ ID NO. 206). This "patch" is referred to herein as "P2". These studies demonstrate that P2 comprises at least one epitope (linear, conformational, or a combination of the same) to which such non-competitive antibodies bind. Given that this region has no previous implication in the functional activity of PD-1, it is proposed herein that binding to P2 represents a novel mechanism of action at a novel site on PD-1 at which antagonistic activity towards PD-1 may be exerted. It is further proposed herein that other antibodies,

antibody fragments, or other protein binding agents that can interact with the P2 region of PD-1 may also act as PD-1 antagonists in a manner distinct from and complementary to anti-PD-1 antibodies that act through blockade of the PD-1/PD-L1 interaction. The binding agents described herein may, for instance, interact with an as yet unidentified ligand; interfere with, induce and/or enhance PD-1 multimerization; and/or, by interacting with (e.g., binding) P2, altering intracellular signaling associated with PD-1. Accordingly, the binding agents described herein that interact with (e.g., bind) P2 may provide the PD-1 antagonistic function through any of these, or any other yet to be identified, mechanisms.

Accordingly, this disclosure provides methods for affecting the function of PD-1 by interacting with this P2 patch of PD-1 in or on a cell. Amino acid residues in the P2 patch of PD-1 may comprise threonine 36, phenylalanine 37, serine 38, proline 39, leucine 41, valine 43, alanine 50, threonine 51, phenylalanine 52, threonine 53, cysteine 54, serine 55, asparagine 102, arginine 104, aspartic acid (aspartate) 105, phenylalanine 106, histidine 107, and methionine 108, the amino acid numbering corresponding to SEQ ID NO. 204. Aspartic acid 85 and/or arginine 86 may also be present in the P2 patch. In some embodiments, the amino acid residues of the P2 patch may comprise threonine 36, phenylalanine 37, alanine 50, threonine 51, phenylalanine 52, threonine 53, cysteine 54, serine 55, aspartic acid (aspartate) 105, phenylalanine 106, histidine 107 and methionine 108, the amino acid numbering corresponding to SEQ ID NO. 204. In some embodiments, the amino acid residues of the P2 patch may comprise amino acid residues serine 38, proline 39, leucine 41, valine 43, asparagine 102, arginine 104, and/or aspartic acid (aspartate) 105. Thus, in some embodiments, the method may comprise interacting with amino acids threonine 36, phenylalanine 37, serine 38, proline 39, leucine 41, valine 43, alanine 50, threonine 51, phenylalanine 52, threonine 53, cysteine 54, serine 55, asparagine 102, arginine 104, aspartic acid (aspartate) 105, phenylalanine 106, histidine 107, and/or methionine 108, the amino acid numbering corresponding to SEQ ID NO. 204. In some embodiments, the method may comprise interacting with amino acids threonine 36, phenylalanine 37, alanine 50, threonine 51, phenylalanine 52, threonine 53, cysteine 54, serine 55, aspartic acid (aspartate) 105, phenylalanine 106, histidine 107 and/or methionine 108. In some embodiments, the method may comprise interacting with amino acid serine 38, proline 39, leucine 41, valine 43, asparagine 102, arginine 104, and/or aspartic acid (aspartate) 105. In some embodiments, the method comprises interacting with any amino acids within and/or overlapping the P2 patch (e.g., portions of PD-1 comprising the above-described amino acid residues). In some embodiments of such methods, the method comprises interacting with one or more amino acid residues corresponding to serine 38, proline 39, and/or leucine 41 of SEQ ID NO. 204 (M4; FIG. **10**; SEQ ID NO. 142); and/or one or more amino acid residues corresponding to asparagine 102 and/or arginine 104 relative to SEQ ID NO. 204 (M17; FIG. **2**; SEQ ID NO. 155); and/or one or more amino acid residues corresponding to aspartic acid (aspartate) 105 relative to SEQ ID NO. 204 (M18; FIG. **10**; SEQ ID NO. 156); and/or one or more amino acid residues corresponding to leucine 41 and/or valine 43 (M31; FIG. **10**; SEQ ID NO. 204). In some such embodiments, the interaction may be decreased and/or eliminated by modifying (e.g., substituting, eliminating) any one or more of such amino acid residues. In some embodiments, the methods comprise antagonistically affecting the function of PD-1. In some embodiments, the methods comprise interacting with PD-1 using a PD-1 binding agent. In some embodiments, the PD-1 binding agent has specificity for a region (e.g., an epitope) comprising one or more of such amino acid residues corresponding such as, for instance, leucine41 and/or valine43 (M4) of SEQ ID NO. 204; and/or one or more amino acid residues corresponding to asparagine102 and/or arginine104 (M17) relative to SEQ ID NO. 204. In some embodiments, the interaction may be involve a binding agent having the ability to bind PD-1 (SEQ ID NO. 204) but not PD-1 M4 (SEQ ID NO. 142), and/or involve a binding agent having the ability to bind PD-1 (SEQ ID NO. 204) but not PD-1 M17 (SEQ ID NO. 155). In some embodiments, the methods may comprise interacting with PD-1 at a site involved in the interaction of PD-1 with PD-L1 and/or PD-L2 (e.g., the P1 patch) and P2. The phrase "one or more amino acid residues corresponding to" an amino acid "of SEQ ID NO. 204" refers to an amino acid in another version of PD-1 similarly positioned as found in SEQ ID NO. 204 (FIG. **10**H). Those of ordinary skill in the art will understand, however, that an amino acid in a PD-1 polypeptide other than SEQ ID NO. 204 (FIG. **10**H) may be determined to "correspond to" a particular amino acid in SEQ ID NO. 204 (FIG. **10**H) by its context within the polypeptide. For instance, monkey PD-1 (SEQ ID NO. 205 (FIG. **10**I)) comprises leucine at position 41, as does SEQ ID NO. 204. But the numbering of another PD-1 may differ due to, for instance, one or more additions, deletions, and/or substitution such that the "corresponding" leucine in that particular PD-1 may be found at, for instance, position 40 or 43. However, that leucine would be understood by those of ordinary skill in the art to "correspond to" leucine 41 relative to its context within SEQ ID NO. 204 (FIG. **10**H) (e.g., it may be surrounded by the amino acids PA and LV as in SEQ ID NO. 204 (FIG. **10**H)). Other embodiments of such methods and amino acids (e.g., one "corresponding to" another) are also contemplated herein, as would be understood by those of ordinary skill in the art.

Binding affinity may be determined by any technique available to those of ordinary skill in the art. The binding affinity data presented in Table 2 was evaluated by flow cytometry staining of endogenous cell surface PD-1 on CD4 T cells that were stimulated for a period of 3 to 6 days with phytohaemagglutinin (PHA). Binding class may also be determined by any technique available to those of ordinary skill in the art. The binding class data presented in Table 2 was determined by Luminex assay competitive binding studies. In Table 2, binding class 1 mAb antibodies are those determined to be competitive with the EH12.2H7 clone commercial antibody (available from BioLegend, San Diego, Calif. (e.g., Cat. No. 329905)); class 2 antibodies are those determined to be competitive with the J116 clone commercial antibody (available from Affymetrix eBioscience, San Diego, Calif. (e.g., Cat. No. 16-9989-80)); and class 3 antibodies are those determined to be competitive with both EH12.2H7 and J116 antibodies; and class 4 mAb clone antibodies are those determined to bind PD-1 in the presence of both EH12.2H7 and J116 antibodies.

Proliferative effect may be determined by any technique available to those of ordinary skill in the art. For instance, the EFRA system described above and used in Example 1 may be used. Such an assay was used to determine the proliferative effect data presented in Table 2. Briefly, a carboxyfluorescein succinimidyl ester (CFSE) assay in which peripheral blood mononuclear cells (PBMCs) were isolated from a chronically infected HIV subject and stimulated with an HIV-specific peptide in the presence and absence of an anti-PD-1 antibody. A control anti-PD1 antibody (the Merck antibody MK-3475) was also tested as a

positive control. Following a six-day incubation, proliferation of HIV-specific CD8 T cells was evaluated in the anti-PD-1 treated samples relative to the peptide alone control and the result expressed as a percentage above control ("Proliferation effect").

In some embodiments, the techniques used to identify and characterize PD-1 binding agents such as antibodies may be combined to provide a system for identifying and characterizing such binding agents. For instance, one or more candidate binding agents such one or more monoclonal antibodies may be assayed by EFRA or a similar assay to determine the ability of the candidate binding agent to restore function to immune cells as measured by, for instance, proliferation in the presence of an immunogenic peptide. In some embodiments, this type of assay may be used as an initial screen to ensure the candidate binding agents to be further studied are capable of restoring immune cell function. In some embodiments, these types of assays may be followed by one for determining the binding affinity to immune cells such as activated peripheral blood mononuclear cells (PBMCs). In some embodiments, this assay may use a technique such as fluorescence activated cell sorting (FACS). In some embodiments, the assay may include the presence or absence of non-specific binding and/or competitive binding studies using known binding reagents such as anti-PD1 antibody (e.g., the Merck antibody MK-3475, also know as pembrolizumab). These assays may then be followed by sequencing of the CDRs of the candidate binding agents such as provided in Tables 1A and/or 1B above. Together, then, the EFRA, affinity determination, epitope mapping studies and CDR identification methods described herein provide a system with which a candidate binding agent may be identified.

Any of the amino acid sequences of Tables 1A and/or 1 B, and/or any of SEQ ID NOS. 170-176, 178-184, 186-193, and/or 195-202 (and/or any one or more fragments and/or derivatives thereof) may be also substituted by any other amino acid as desired by one of ordinary skill in the art. For example, one of skill in the art may make conservative substitutions by replacing particular amino acids with others as shown in Table 3 below. The specific amino acid substitution selected may depend on the location of the site selected. Such conservative amino acid substitutions may involve a substitution of a native amino acid residue with a non-native residue such that there is little or no effect on the size, polarity, charge, hydrophobicity, or hydrophilicity of the amino acid residue at that position and, in particular, does not result in decreased PD-1 binding.

TABLE 3

Original Amino Acid Residues in SEQ ID NOS. 1-138	Exemplary Conservative Substitutions of the Original Amino Acid Residues of SEQ ID NOS. 1-138	Preferred ConservativeSubstitution of the Original Amino Acid Residues of SEQ ID NOS. 1-138
Ala	Val, Leu, Ile	Val
Arg	Lys, Gln, Asn	Lys
Asn	Gln	Gln
Asp	Glu	Glu
Cys	Ser, Ala	Ser
Gln	Asn	Asn
Glu	Asp	Asp
Gly	Pro, Ala	Ala
His	Asn, Gln, Lys, Arg	Arg
Ile	Leu, Val, Met, Ala, Phe, Norleucine	Leu
Leu	Norleucine, Ile, Val, Met, Ala, Phe	Ile
Lys	Arg, 1,4 Diamino-butyric Acid, Gln, Asn	Arg
Met	Leu, Phe, Ile	Leu
Phe	Leu, Val, Ile, Ala, Tyr	Leu
Pro	Ala	Gly
Ser	Thr, Ala, Cys	Thr
Thr	Ser	Ser
Trp	Tyr, Phe	Tyr
Tyr	Trp, Phe, Thr, Ser	Phe
Val	Ile, Met, Leu, Phe, Ala, Norleucine	Leu

In some embodiments, this disclosure provides binding agents with multiple specificities such that PD-1 and at least one other secondary antigen (e.g., a cell surface protein) may be bound by a single binding agent. In some embodiments, the secondary antigen may be one expressed by cells infected by an infectious agent. For instance, an exemplary secondary antigen may be HIV Env antigen. Such binding agents may bind the secondary antigen and/or may serve to neutralize the infectious agent. In certain embodiments, such as for a bi-specific binding agent having dual specificity for PD-1 and an HIV antigen such as env and/or another antigen, for instance. The HIV immunogen may be derived from any of the subtypes described herein, or any other. In some embodiments, such binding agents may include: PD-1 agonist/Env binding; PD-1 agonist PD-1/Env binding and neutralization; PD-1 antagonist/Env binding; and/or PD-1 antagonist/PD-1/Env binding and neutralization. Given the prevelance of the various subtypes, it may be preferable to select antigens from HIV-1 subtypes B and/or C. It may also be desirable to include binding agents having specificity for antigens from multiple HIV subtypes (e.g., HIV-1 subtypes B and C, HIV-2 subtypes A and B, or a combination of HIV-1 and HIV-2 subtypes) in a single composition. For treating a disease such as cancer, it may be beneficial to obtain binding agents with multiple PD-1 specificities (e.g., bi-specific PD-1a/PD1b antagonist PD-1 antibodies specific to two different epitopes) and/or specificity to both PD-1 and one or more tumor antigens (e.g., cancer-testis (CT) antigen (i.e., MAGE, NY-ESO-1); melanocyte differentiation antigen (i.e., Melan A/MART-1, tyrosinase, gp100); mutational antigen (i.e., MUM-1, p53, CDK-4); overexpressed 'self' antigen (i.e., HER-2/neu, p53); and/or viral antigens (i.e., HPV, EBV)). The binding agents (e.g., monoclonal antibodies) may be generated as generally described above. The specificities of such binding agents may be recombined into a single binding agent using techniques that are widely available to those of ordinary skill in the art. In some embodiments, multiple single specifity binding agents may also be combined and used (e.g., administered) to provide an effective multiple specificity reagent.

In some embodiments, the binding agents described herein may be conjugated to active agents to target and inhibit the function of and/or eliminate cell populations expressing PD-1 (and/or another antigen in the case of binding agents with multiple specificities). For instance, $CD4^+$ T-cell populations containing replication competent HIV may be targeted and eliminated using binding agent/drug conjugates (e.g., antibody-drug conjugates (ADC)). Mono- and/or bi-specific candidate binding agents may be

conjugated with one or more types of drugs (e.g., drugs damaging DNA, targeting microtubules). The binding agents described herein and/or derivatives thereof may also be adjoined to and/or conjugated to functional agents for in vitro and/or in vivo use. For instance, the binding agent may be adjoined to and/or conjugated to functional moieties such as cytotoxic drugs or toxins, and/or active fragments thereof such as diphtheria A chain, exotoxin A chain, ricin A chain, abrin A chain, curcin, crotin, phenomycin, enomycin, among others. Suitable functional moieties may also include radiochemicals. Binding agents, such as antibodies, may be adjoined to and/or conjugated to the one or more functional agents using standard techniques in the art.

In some embodiments, the binding agents may be administered in conjunction with other agents such as anti-infective agents (e.g., antibiotics, anti-viral medications). For instance, the binding agents described herein may be combined with monoclonal antibodies and/or other reagents such as Nivolumab (also known as MDX-1106, BMS-936558 (Topalian, et al. N. Eng. J. Med. 2012; 366(26): 2443-2454), MDX-1106, ONO-4538, a fully human IgG4 mAb available from Bristol-Myers Squibb), Lambrolizumab (also known as MK-3475 and SCH 900475, a humanized IgG4 monoclonal antibody available from Merck), Pidilizumab (a humanized IgG1 monoclonal antibody available from CureTech), AMP-224 (a B7-DC/IgG1 fusion protein available from GlaxoSmithKline/Amplimmune), and/or an antibody or other reagent or method described in any of U.S. Pat. No. 8,354,509B2 (Carven, et al), U.S. Pat. No. 8,008,449B2 (Korman, et al), WO 2012/135408A1 (Manoj, et al.), US 2010/026617 (Carven, et al.), WO 2011/110621A1 (Tyson, et al), U.S. Pat. No. 7,488,802B2 (Collins, et al.), WO 2010/029435A1 (Simon, et al.), WO 2010/089411A2 (Olive, D.), WO 2012/145493A1 (Langermann, et al.), WO 2013/0435569A1 (Rolland, et al.), WO 2011/159877A2 (Kuchroo, et al.), U.S. Pat. No. 7,563,869B2 (Ono Pharm.), U.S. Pat. No. 7,858,746B2 (Honjo, et al.), U.S. Pat. No. 8,728,474B2 (Ono Pharm.), U.S. Pat. No. 9,067,999 (Ono Pharm.), and/or U.S. Pat. No. 9,067,999, each of which is hereby incorporated in its entirety into this disclosure. According to a preferred embodiment, any of the PD-1 binding agents may be fused to other binding agents to form bi-specific binding molecules, in particular bi-specific antibodies. Such bi-specific molecules advantageously couple the PD1 binding agent with another PD1 binding agent, or with another binding agent that targets checkpoint inhibitors or modulators, in particular CTLA-4, LAG3, TIM3, CD137, 4-1BB, OX40, CD27, GITR (Glucocorticoid-induced Tumor Necrosis Factor), CD40, KIR, IDO IL-2, IL-21 and CSF-1R (Colony Stimulatory Factor 1 Receptor). Other combinations and/or bi-specific binding molecules are also contemplated herein, as would be understood by those of ordinary skill in the art.

As mentioned above, the PD-1 binding agents described herein (e.g., a PD-1 antagonist) may be used to treat and/or prevent and/or ameliorate the symptoms of infection by HIV. As is well-known in the art, HIV isolates are now classified into discrete genetic subtypes. HIV-1 is known to comprise at least ten subtypes (A1, A2, A3, A4, B, C, D, E, F1, F2, G, H, J and K) (Taylor et al, NEJM, 359(18):1965-1966 (2008)). HIV-2 is known to include at least five subtypes (A, B, C, D, and E). Subtype B has been associated with the HIV epidemic in homosexual men and intravenous drug users worldwide. Most HIV-1 immunogens, laboratory adapted isolates, reagents and mapped epitopes belong to subtype B. In sub-Saharan Africa, India and China, areas where the incidence of new HIV infections is high, HIV-1 subtype B accounts for only a small minority of infections, and subtype HIV-1 C appears to be the most common infecting subtype. Any of these types of isolates may be addressed using the binding agents described herein. One or more binding agents may also be administered with or in conjunction with one or more agents used to prevent, treat and/or ameliorate HIV such as for example, a protease inhibitor, an HIV entry inhibitor, a reverse transcriptase inhibitor, and/or an anti-retroviral nucleoside analog. Suitable compounds include, for example, Agenerase (amprenavir), Combivir (Retrovir/Epivir), Crixivan (indinavir), Emtriva (emtricitabine), Epivir (3tc/lamivudine), Epzicom, Fortovase/Invirase (saquinavir), Fuzeon (enfuvirtide), Hivid (ddc/zalcitabine), Kaletra (lopinavir), Lexiva (Fosamprenavir), Norvir (ritonavir), Rescriptor (delavirdine), Retrovir/AZT (zidovudine), Reyatax (atazanavir, BMS-232632), Sustiva (efavirenz), Trizivir (abacavir/zidovudine/lamivudine), Truvada (Emtricitabine/Tenofovir DF), Videx (ddI/didanosine), Videx EC (ddI, didanosine), Viracept (nevirapine), Viread (tenofovir disoproxil fumarate), Zerit (d4T/stavudine), and Ziagen (abacavir) may be utilized. Other suitable agents are known to those of skill in the art and may be suitable for use as described herein. Such agents may either be used prior to, during, or after administration of the binding agents and/or use of the methods described herein.

As mentioned above, the PD-1 binding agents described herein (e.g., a PD-1 antagonist) may be used to treat and/or prevent and/or ameliorate the symptoms of cancer. Exemplary cancers may include, for instance, any of the breast, blood, colon, stomach, rectum, skeletal tissue, skin (e.g., melanoma) brain, lung, bladder, kidney, ovary, and/or liver, among others. In addition, the PD-1 binding agents described herein, preferably the antibodies that are non-competitive or only partially competitive with respect to the PD-1/PDL-1 interaction, in particular those referred to herein as binding Class II, such as but not limited to 135C12, 139D6, 136B4 and 135D1, are particularly useful, alone or in combination with one another and/or other PD-1 antibodies, for treating various types of malignancies, in particular melanoma (e.g., metastatic malignant melanoma), renal cancer (e.g., clear cell carcinoma), bladder cancer, prostate cancer (e.g., castration resistant prostate cancer), pancreatic cancer, breast cancer, colon cancer, lung cancer (e.g., non-small cell lung cancer), esophageal cancer, squamous cell carcinoma of the head and neck, Merkel cell carcinoma, liver cancer, ovarian cancer, cervical cancer, thyroid cancer, glioblastoma, glioma, leukemia, lymphoma, sarcomas and other neoplastic malignancies. The above preferred PD-1 binding agents are more particularly dedicated to the treatment of hematological malignancies such as Hodgkin's disease, Non-Hodgkin's Lymphoma such as Follicular lymphoma, Diffuse large B cell lymphoma, Multiple myeloma (MM), Acute myeloid leukemia (AML), Acute Lymphoblastic leukemia (ALL), and myelodysplastic syndromes. The binding agents described herein may be used to treat other types of cancers as well, as would be understood by those of ordinary skill in the art.

In some embodiments, one or more of the PD-1 binding agents may also be combined with and/or administered with or in conjunction with one or more agents used to prevent, treat and/or ameliorate cancer such as for example, an alkylating agent (e.g., any nitrogen mustard, nitrosourea, tetrazine, aziridine, cisplatin and/or derivative thereof), antimetabolite (e.g., any of the methotrexates, pemetrexeds, fluoropyrimidines and/or derivative thereof), anti-microbtubule agent (e.g., vinca alkyloids, taxanes, podophyllotoxin and/or derivative thereof), topoisomerase I and/or II inhibi-

tors (e.g., a camptothecin, irinotecan, topotecan, etoposide, doxorubicin, mitoxantrone, teniposide, novobiocin, merbarone, aclarubicin and/or derivative thereof) and/or cytotoxic antibiotic (e.g., any anthracyclines, actinomycin, bleomycin, plicamycin, and mitomycin and/or derivative thereof). The one or more binding agents may also, or alternatively, be combined with one or more other binding agents available to those of ordinary skill in the art for treating, preventing and/or ameliorating cancer such as, for example, Nivolumab, Lambrolizumab, Pidilizumab and/or other similar agents and/or derivatives thereof. The one or more PD-1 binding agents may also be used alone or in combination with other binding agents targeting PD-1, PDL-1 and/or other immune checkpoints effectors. These may also be used in combination with other anti-neoplastic agents or immunogenic agents (for example, attenuated cancerous cells, tumor antigens (including recombinant proteins, peptides, and carbohydrate molecules), antigen presenting cells such as dendritic cells pulsed with tumor derived antigen or nucleic acids, immune stimulating cytokines (for example, IL-2, IFNa2, GM-CSF), and/or cells transfected with genes encoding immune-stimulating cytokines such as but not limited to GM-CSF; standard cancer treatments (for example, chemotherapy, radiotherapy or surgery); or other agents directed to VEGF, EGFR, Her2/neu, VEGF receptors, other growth factor receptors. According to a preferred embodiment, the one or more PD-1 binding agents is combined with vaccine agents and/or immune checkpoint modulators acting more particularly on CTLA-4, LAG3, TIM3, CD137, 4-1BB, OX40, CD27, GITR (Glucocorticoid-induced Tumor Necrosis Factor), CD40, KIR, IDO IL-2, IL-21 and/or CSF-1 R (Colony Stimulatory Factor 1 Receptor) to form a therapeutic composition and/or a kit for sequential therapeutic administration. Other suitable agents are known to those of skill in the art and may be suitable for use as described herein. Such agents may either be used prior to, during, or after administration of the binding agents and/or use of the methods described herein.

As mentioned above, the PD-1 binding agents described herein (e.g., a PD-1 agonist) may be used to treat and/or prevent and/or ameliorate the symptoms of autoimmunity. Exemplary autoimmune conditions may include, for instance, any in which PD-1 is involved in maintaining self-tolerance and/or one involving inflammatory T cells (e.g., autoreactive or self antigen-specific T cells) such as, for instance, systemic lupus erythematosus (SLE), type I diabetes, rheumatoid arthritis, glomerulonephritis, and multiple sclerosis. Such PD-1 binding agents may also be combined with other agents such as anti-CTLA-4 agents (e.g., ipilimumab). One or more of the binding agents may also be combined with and/or administered with or in conjunction with one or more agents used to prevent, treat and/or ameliorate autoimmunity such as, for example, glucocorticoids, cytostatics (e.g., alkylating agent, anti-metabolite, methotrexate, azathioprine, mercaptopurine, cytotoxic antibiotics (e.g., dactinomycin, anthracyclines, mitomycin C, bleomycin, mithramycin), antibodies (e.g., Atgam, Thymoglobuline, Simulect, Zenapax), drugs acting on immunophilins (e.g., ciclosporin, tacrolimus, sirolimus), interferons, opioids, TNF-binding agents (e.g., Remicade, Enbrel, Humira), mycophenolate, fingolimod, myriocin, and/or derivatives thereof. Other suitable agents are known to those of skill in the art and may be suitable for use as described herein. Such agents may either be used prior to, during, or after administration of the binding agents and/or use of the methods described herein.

In some embodiments, the binding agents may be adjoined to and/or conjugated to one or more detectable labels. For instance, suitable detectable labels may include, for instance, fluorosceins (e.g., DyLight, Cy3, Cy5, FITC, HiLyte Fluor 555, HiLyte Fluor 647; 5-carboxy-2,7-dichlorofluorescein; 5-Carboxyfluorescein (5-FAM); 5-HAT (Hydroxy Tryptamine); 5-Hydroxy Tryptamine (HAT); 6-JOE; 6-carboxyfluorescein (6-FAM); FITC; 6-carboxy-1,4-dichloro-2',7'-dichlorofluorescein (TET); 6-carboxy-1,4-dichloro-2',4',5',7'-tetra-chlorofluorescein (HEX); 6-carboxy-4',5'-dichloro-2',7'-dimethoxyfluorescein (JOE); Alexa fluors (e.g., 350, 405, 430, 488, 500, 514, 532, 546, 555, 568, 594, 610, 633, 635, 647, 660, 680, 700, 750); BODIPY fluorophores (e.g., 492/515, 493/503, 500/510, 505/515, 530/550, 542/563, 558/568, 564/570, 576/589, 581/591, 630/650-X, 650/665-X, 665/676, FL, FL ATP, FI-Ceramide, R6G SE, TMR, TMR-X conjugate, TMR-X, SE, TR, TR ATP, TR-X SE)), rhodamines (e.g., 110, 123, B, B 200, BB, BG, B extra, 5-carboxytetramethylrhodamine (5-TAMRA), 5 GLD, 6-Carboxyrhodamine 6G, Lissamine, Lissamine Rhodamine B, Phallicidine, Phalloidine, Red, Rhod-2, ROX (6-carboxy-X-rhodamine), 5-ROX (carboxy-X-rhodamine), Sulphorhodamine B can C, Sulphorhodamine G Extra, TAMRA (6-carboxytetramethylrhodamine), Tetramethylrhodamine (TRITC), WT), Texas Red, and/or Texas Red-X. Other detectable labels known in the art may also be suitable for use. Binding agents, such as antibodies, may be adjoined to and/or conjugated to the one or more detectable labels using standard techniques in the art.

In certain embodiments, a nucleic acid molecule encoding one or more binding agents described herein may be inserted into one or more expression vectors, as discussed below in greater detail. In such embodiments, the binding agent may be encoded by nucleotides corresponding to the amino acid sequence. The particular combinations of nucleotides (codons) that encode the various amino acids (AA) are well known in the art, as described in various references used by those skilled in the art (e.g., Lewin, B. *Genes V,* Oxford University Press, 1994). The nucleotide sequences encoding the amino acids of said binding agents may be ascertained with reference to Table 4, for example. Nucleic acid variants may use any combination of nucleotides that encode the binding agent.

TABLE 4

Codons Encoding Amino Acids (AA) of SEQ ID NOS. 1-138 of Variants Thereof

AA	Codon	AA	Codons	AA	Codons	AA	Codons
Phe (F)	TTT	Ser (S)	TCT	Tyr (Y)	TAT	Cys (C)	TGT
	TTC		TCC		TAC		TGC
Leu (L)	TTA		TCA	TERM	TAA	TERM	TGA
	TTG		TCG		TAG	Trp (W)	TGG
	CTT	Pro (P)	CCT	His (H)	CAT	Arg (R)	CGT
	CTC		CCC		CAC		CGC
	CTA		CCA	Gln (Q)	CAA		CGA
	CTG		CCG		CAG		CGG

TABLE 4-continued

Codons Encoding Amino Acids (AA) of SEQ ID NOS. 1-138 of Variants Thereof

AA	Codon	AA	Codons	AA	Codons	AA	Codons
Ile (I)	ATT	Thr (T)	ACT	Asn (N)	AAT	Ser (S)	AGT
	ATC		ACC		AAC		AGC
	ATA		ACA	Lys (K)	AAA	Arg (R)	AGA
Met (M)	ATG		ACG		AAG		AGG
Val (V)	GTT	Ala (A)	GCT	Asp (D)	GAT	Gly (G)	GGT
	GTC		GCC		GAC		GGC
	GTA		GCA	Glu (E)	GAA		GGA
	GTG		GCG		GAG		GGG

Those of ordinary skill in the art understand that the nucleotide sequence encoding a particular amino acid sequence may be easily derived from the amino acid sequence and the information presented in Table 4. For instance, it may be deduced from the amino acid sequence DDFLH (SEQ ID NO.: 1) and the information presented in Table 4 that the amino acid sequence may be encoded by the nucleotide sequence GAT GAT TTT TTA CAT (SEQ ID NO.:203). Those of ordinary skill in the art would understand that nucleotide sequences encoding SEQ ID NOS. 2-138, 170-176, 178-184, 186-193, and/or 195-202 may be deduced in the same way, and such nucleotide sequences are contemplated herein. Where the binding agents are antibodies, nucleotide sequences encoding the variable regions thereof may also be isolated from the phage and/or hybridoma cells expressing the same cloned into expression vectors to produce certain preparations (e.g., humanized antibodies). Methods for producing such preparations are well-known in the art.

To determine the amino acid sequences of the variable regions (e.g., CDRs) of interest, hybridoma cells from mice immunized with a PD-1 antigen/immunogen may be selected using the functional assays described herein and cloning techniques that are readily available to those of ordinary skill in the art. For instance, to isolate and sequence nucleic acids encoding the heavy and light chain variable regions of the selected hybridomas, total RNA may be extracted from fresh hybridoma cells using TRIzol reagent according to the manufacturer's protocol. cDNA may be synthesized from the RNA using isotype-specific anti-sense primers or universal primers using standard techniques (e.g., following the technical manual of PrimeScript™ 1st Strand cDNA Synthesis Kit). Polymerase chain reaction (PCR) may then be performed to amplify the nucleic acids encoding the variable regions (heavy and light chains) of the antibody produced by the selected hybridoma, which may then be cloned into a standard cloning vector separately and sequenced. Colony PCR screening may then be performed to identify clones with inserts of correct sizes. Preferably, no less than five single colonies with inserts of correct sizes are sequenced for each antibody variable region. Standard protocols may then be used for the expression and purification of the anti-PD-1 antibodies. For instance, hybridoma clones may be grown in serum-free medium and the cell culture broth centrifuged and then filtered. The filtered supernatant containing the antibody may then be loaded onto an affinity column (e.g., Protein A) column, washed and eluted with an appropriate buffer (e.g., Pierce IgG elute buffer). The eluted fractions may then be pooled and buffer-exchanged into PBS, pH 7.2. The purified antibody may then be analyzed by SDS-PAGE and Western blot by using standard protocols for molecular weight, yield and purity. Size exclusion chromatography HPLC may then be performed on an appropriate column (e.g., TSK GEL-G3000 SWXL column (Tosoh)) for biophysical characterization in order to ensure high antibody purity (generally >90%) with low presence of protein aggregates. These procedures were used in isolating and sequencing nucleic acids encoding SEQ ID NOS. 1-138, 170-176, 178-184, 186-193, and/or 195-202 from selected cells. These techniques, variations thereof, and/or other may also be of use for these purposes as would be understood by those of ordinary skill in the art.

Nucleic acid molecules encoding one or more PD-1 binding agents may be contained within a viral and/or a non-viral vector. In one embodiment, a DNA vector is utilized to deliver nucleic acids encoding one or more PD-1 binding agents to the patient. In doing so, various strategies may be utilized to improve the efficiency of such mechanisms including, for example, the use of self-replicating viral replicons (Caley, et al. 1999. *Vaccine,* 17: 3124-2135; Dubensky, et al. 2000. *Mol. Med.* 6: 723-732; Leitner, et al. 2000. *Cancer Res.* 60: 51-55), codon optimization (Liu, et al. 2000. *Mol. Ther.,* 1: 497-500; Dubensky, supra; Huang, et al. 2001. *J. Virol.* 75: 4947-4951), in vivo electroporation (Widera, et al. 2000. *J. Immunol.* 164: 4635-3640), incorporation of nucleic acids encoding co-stimulatory molecules, cytokines and/or chemokines (Xiang, et al. 1995. *Immunity,* 2: 129-135; Kim, et al. 1998. *Eur. J. Immunol.,* 28: 1089-1103; Iwasaki, et al. 1997. *J. Immunol.* 158: 4591-3601; Sheerlinck, et al. 2001. *Vaccine,* 19: 2647-2656), incorporation of stimulatory motifs such as CpG (Gurunathan, supra; Leitner, supra), sequences for targeting of the endocytic or ubiquitin-processing pathways (Thomson, et al. 1998. *J. Virol.* 72: 2246-2252; Velders, et al. 2001. *J. Immunol.* 166: 5366-5373), prime-boost regimens (Gurunathan, supra; Sullivan, et al. 2000. *Nature,* 408: 605-609; Hanke, et al. 1998. *Vaccine,* 16: 439-445; Amara, et al. 2001. Science, 292: 69-74), proteasome-sensitive cleavage sites, and the use of mucosal delivery vectors such as *Salmonella* (Darji, et al. 1997. *Cell,* 91: 765-775; Woo, et al. 2001. *Vaccine,* 19: 2945-2954). Other methods are known in the art, some of which are described below. Various viral vectors that have been successfully utilized for introducing a nucleic acid to a host include retrovirus, adenovirus, adeno-associated virus (AAV), herpes virus, and poxvirus, among others. The vectors may be constructed using standard recombinant techniques widely available to one skilled in the art. Such techniques may be found in common molecular biology references such as *Molecular Cloning: A Laboratory Manual* (Sambrook, et al., 1989, Cold Spring Harbor Laboratory Press), *Gene Expression Technology* (Methods in Enzymology, Vol. 185, edited by D. Goeddel, 1991. Academic Press, San Diego, Calif.), and *PCR Protocols: A Guide to Methods and Applications* (Innis, et al. 1990. Academic Press, San Diego, Calif.). "Non-viral" plasmid vectors may also be suitable in certain embodiments. Pre-

ferred plasmid vectors are compatible with bacterial, insect, and/or mammalian host cells. Such vectors include, for example, PCR-ii, PCR3, and pcDNA3.1 (Invitrogen, San Diego, Calif.), pBSii (Stratagene, La Jolla, Calif.), pet15 (Novagen, Madison, Wis.), pGEX (Pharmacia Biotech, Piscataway, N.J.), pEGFp-n2 (Clontech, Palo Alto, Calif.), pETI (Bluebacii, Invitrogen), pDSR-alpha (PCT pub. No. WO 90/14363) and pFASTBACdual (Gibco-BRL, Grand island, N.Y.) as well as Bluescript® plasmid derivatives (a high copy number COLe1-based phagemid, Stratagene Cloning Systems, La Jolla, Calif.), PCR cloning plasmids designed for cloning TAQ-amplified PCR products (e.g., TOPO™ TA cloning® kit, PCR2.1® plasmid derivatives, Invitrogen, Carlsbad, Calif.). Bacterial vectors may also be used. These vectors include, for example, *Shigella, Salmonella, Vibrio cholerae, Lactobacillus, Bacille Calmette Guérin* (BCG), and *Streptococcus* (see for example, WO 88/6626; WO 90/0594; WO 91/13157; WO 92/1796; and WO 92/21376). Many other non-viral plasmid expression vectors and systems are known in the art and may be use. Other delivery techniques may also suffice including, for example, DNA-ligand complexes, adenovirus-ligand-DNA complexes, direct injection of DNA, CaPO4 precipitation, gene gun techniques, electroporation, and colloidal dispersion systems. Colloidal dispersion systems include macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. The preferred colloidal system is a liposome, which are artificial membrane vesicles useful as delivery vehicles in vitro and in vivo. RNA, DNA and intact virions can be encapsulated within the aqueous interior and be delivered to cells in a biologically active form (Fraley, R., et al., 1981, *Trends Biochem. Sci.,* 6: 77). The composition of the liposome is usually a combination of phospholipids, particularly high-phase-transition-temperature phospholipids, usually in combination with steroids, especially cholesterol. Other phospholipids or other lipids may also be used. The physical characteristics of liposomes depend on pH, ionic strength, and the presence of divalent cations. Examples of lipids useful in liposome production include phosphatidyl compounds, such as phosphatidylglycerol, phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, sphingolipids, cerebrosides, and gangliosides. Particularly useful are diacylphosphatidylglycerols, where the lipid moiety contains from 14-18 carbon atoms, particularly from 16-18 carbon atoms, and is saturated. Illustrative phospholipids include egg phosphatidylcholine, dipalmitoylphosphatidylcholine and distearoylphosphatidylcholine.

A cultured cell comprising the vector is also provided. The cultured cell may be a cultured cell transfected with the vector or a progeny of the cell, wherein the cell expresses the immunogenic polypeptide. Suitable cell lines are known to those of skill in the art and are commercially available, for example, through the American Type Culture Collection (ATCC). The transfected cells can be used in a method of producing an immunogenic polypeptide. The method comprises culturing a cell comprising the vector under conditions that allow expression of the immunogenic polypeptide, optionally under the control of an expression sequence. The immunogenic polypeptide can be isolated from the cell or the culture medium using standard protein purification methods.

The skilled artisan has many suitable techniques for using the binding agents (e.g., antibodies) described herein to identify biological samples containing proteins that bind thereto. For instance, antibodies may be utilized to isolate PD-1 using, for example, immunoprecipitation or other capture-type assay. This well-known technique is performed by attaching the antibody to a solid support or chromatographic material (e.g., a bead coated with Protein A, Protein G and/or Protein L). The bound antibody is then introduced into a solution either containing or believed to contain the PD-1 (e.g., an HIV-infected T cell lysate). PD-1 may then bind to the antibody and non-binding materials are washed away under conditions in which the PD-1 remains bound to the antibody. The bound protein may then be separated from the antibody and analyzed as desired. Similar methods for isolating a protein using an antibody are well-known in the art. The binding agents (e.g., antibodies) may also be utilized to detect PD-1 within a biological sample. For instance, the antibodies may be used in assays such as, for example, flow cytometric analysis, ELISA, immunoblotting (e.g., western blot), in situ detection, immunocytochemistry, and/or immunhistochemistry. Methods of carrying out such assays are well-known in the art.

The binding agents described herein may be also be used to determine the presence of a disease state in a patient, to predict prognosis, or to determine the effectiveness of a chemotherapeutic or other treatment regimen. Expression profile assays, performed as described herein or as is otherwise known in the art, may be used to determine the relative level of expression of PD-1. The level of expression may then be correlated with base (e.g., control) levels to determine whether a particular disease is present within the patient, the patient's prognosis, or whether a particular treatment regimen is effective. For example, if the patient is being treated with a particular anti-infective regimen, an increased or decreased level of expression of PD-1 in the patient's tissues (e.g., in peripheral blood, breast tissue biopsy) may indicate the regimen is worsening or improving the load of the infectious agent in that host. The increase or decrease in expression may indicate the regimen is having or not having the desired effect and another therapeutic modality may therefore be selected.

It is also possible to use the binding agents described herein as reagents in drug screening assays to test, for example, new drug candidates. The reagents may be used to ascertain the effect of a drug candidate on the expression of the immunogenic target in a cell line, or a cell or tissue of a patient. The expression profiling technique may be combined with high throughput screening techniques to allow rapid identification of useful compounds and monitor the effectiveness of treatment with a drug candidate (see, for example, Zlokarnik, et al., Science 279, 84-8 (1998)). Drug candidates may be chemical compounds, nucleic acids, proteins, antibodies, or derivatives therefrom, whether naturally occurring or synthetically derived. Drug candidates thus identified may be utilized, among other uses, as pharmaceutical compositions for administration to patients or for use in further screening assays.

In some embodiments, the binding agents are in purified form. A "purified" binding agent (e.g., antibody) may be one that is separated from at least about 50% of the proteins and/or other components with which it is initially found (e.g., as part of a hybridoma supernatant or ascites preparation in the case of a monoclonal antibody). A purified binding agent (e.g., antibody) may be one that is separated from at least about 50%, 60%, 75%, 90%, or 95% of the proteins and/or other components with which it is initially found.

The polypeptides and nucleic acids described herein may be combined with one or more pharmaceutically acceptable carriers prior to administration to a host. A pharmaceutically

acceptable carrier is a material that is not biologically or otherwise undesirable, e.g., the material may be administered to a subject, without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained. The carrier would naturally be selected to minimize any degradation of the active ingredient and to minimize any adverse side effects in the subject, as would be well known to one of skill in the art. Suitable pharmaceutical carriers and their formulations are described in, for example, *Remington's: The Science and Practice of Pharmacy,* 21st *Edition,* David B. Troy, ed., Lippicott Williams & Wilkins (2005). Typically, an appropriate amount of a pharmaceutically-acceptable salt is used in the formulation to render the formulation isotonic. Examples of the pharmaceutically-acceptable carriers include, but are not limited to, sterile water, saline, buffered solutions like Ringer's solution, and dextrose solution. The pH of the solution is generally from about 5 to about 8 or from about 7 to about 7.5. Other carriers include sustained-release preparations such as semipermeable matrices of solid hydrophobic polymers containing polypeptides or fragments thereof. Matrices may be in the form of shaped articles, e.g., films, liposomes or microparticles. It will be apparent to those persons skilled in the art that certain carriers may be more preferable depending upon, for instance, the route of administration and concentration of composition being administered. Carriers are those suitable for administration of polypeptides and/or fragments thereof to humans or other subjects. Pharmaceutical compositions may also include carriers, thickeners, diluents, buffers, preservatives, surface active agents, adjuvants, immunostimulants, in addition to the immunogenic polypeptide. Pharmaceutical compositions may also include one or more active ingredients such as antimicrobial agents, antiinflammatory agents and anesthetics. The pharmaceutical composition may be administered orally, parentally, by inhalation spray, rectally, intranodally, or topically in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles. The term "pharmaceutically acceptable carrier" or "physiologically acceptable carrier" as used herein refers to one or more formulation materials suitable for accomplishing or enhancing the delivery of a nucleic acid, polypeptide, or peptide as a pharmaceutical composition. A "pharmaceutical composition" is a composition comprising a therapeutically effective amount of a nucleic acid or polypeptide. The terms "effective amount" and "therapeutically effective amount" each refer to the amount of a binding agent, nucleic acid or the like used to observe the desired therapeutic effect (e.g., restore T cell function).

Methods for treating one or more disease conditions (e.g., HIV or cancer) in a mammalian host comprising administering to the mammal at least one or more effective doses of one or more binding agents (and/or derivative(s) thereof) described herein are also provided. In some embodiments, the binding agent is a monoclonal antibody or fragment or derivative thereof comprising one or more of SEQ ID NOS. 1-138, 170-176, 178-184, 186-193, and/or 195-202, and/or shown in Tables 1A and 1B. The one or more binding agents may be administered in a dosage amount of about 1 to about 50 mg/kg, about 1 to about 30 mg/kg, or about 5 to about 30 mg/kg (e.g., about any of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, or 40 mg/kg). In certain embodiments, the one or more binding agents may be administered to the mammal (e.g., intradermally, intravenously, orally, rectally) at about 10 mg/kg one or more times. When multiple doses are administered, the doses may comprise about the same or different amount of binding agent in each dose. The doses may also be separated in time from one another by the same or different intervals. For instance, the doses may be separated by about any of 6, 12, 24, 36, 48, 60, 72, 84, or 96 hours, one week, two weeks, three weeks, one month, two months, three months, four months, five months, six months, seven months, eight months, nine months, 10 months, 11 months, 12 months, 1.5 years, 2 years, 3 years, 4 years, 5 years, or any time period before, after, and/or between any of these time periods. In some embodiments, the binding agents may be administered in conjunction with other agents (e.g., anti-infective agents and/or chemotherapeutic agent). Such other agents may be administered about simultaneously with the binding agents, or at a different time and/or frequency. Other embodiments of such methods may also be appropriate as could be readily determined by one of ordinary skill in the art.

To assist the skilled artisan in using the antibodies described herein, the same may be provided in kit format. A kit including such antibodies and optionally other components necessary for using the antibodies to detect cells expressing PD-1 is provided. The antibodies of the kit may be provided in any suitable form, including frozen, lyophilized, or in a pharmaceutically acceptable buffer such as TBS or PBS. The kit may also include other reagents required for utilization of the antibodies in vitro or in vivo such as buffers (e.g., TBS, PBS), blocking agents (solutions including nonfat dry milk, normal sera, Tween-20 Detergent, BSA, or casein), and/or detection reagents (e.g., goat anti-mouse IgG biotin, streptavidin-HRP conjugates, allophycocyanin, B-phycoerythrin, R-phycoerythrin, peroxidase, detectable labels, and other labels and/or staining kits (e.g., ABC Staining Kit, Pierce)). The kits may also include other reagents and/or instructions for using the antibodies in commonly utilized assays described above such as, for example, flow cytometric analysis, ELISA, immunoblotting (e.g., western blot), in situ detection, immunocytochemistry, immunhistochemistry. In one embodiment, the kit provides a binding agent in purified form. In another embodiment, the binding agent may be provided in biotinylated form either alone or along with an avidin-conjugated detection reagent (e.g., antibody). In another embodiment, the kit includes a binding agents comprising one or more detectable labels that may be used to directly detect PD-1. Buffers and the like required for using any of these systems are well-known in the art and/or may be prepared by the end-user or provided as a component of the kit. The kit may also include a solid support containing positive- and negative-control protein and/or tissue samples. For example, kits for performing spotting or western blot-type assays may include control cell or tissue lysates for use in SDS-PAGE or nylon or other membranes containing pre-fixed control samples with additional space for experimental samples. Kits for visualization of PD-1 in cells on slides may include pre-formatted slides containing control cell or tissue samples with additional space for experimental samples. Other embodiments of kits are also contemplated herein as would be understood by those of ordinary skill in the art.

Thus, this disclosure provides a binding agent that binds PD-1 agonistically or antagonistically. In some embodiments, the binding agent is a polypeptide comprising at least one amino acid sequence selected from the group consisting of SEQ ID NOS. 1-138, 170-176, 178-184, 186-193, and/or 195-202 and/or shown in Tables 1A and 1B. In some embodiments, the binding agent is a polypeptide comprising one or more combinations of SEQ ID NOS. 1-138 (e.g., as

shown in Tables 1A and/or 1B), and/or any of SEQ ID NOS. 170-176, 178-184, 186-193, and/or 195-202. In some embodiments, the binding agent is an antibody. In some embodiments, the binding agent is a polypeptide such as an antibody comprising a heavy chain CDR1 amino acid sequence selected from the group consisting of SEQ ID NOS. 1-23. In some embodiments, the binding agent is a polypeptide such as an antibody comprising a heavy chain CDR2 amino acid sequence selected from the group consisting of SEQ ID NOS. 24-46. In some embodiments, the binding agent is a polypeptide such as an antibody comprising a heavy chain CDR3 amino acid sequence selected from the group consisting of 47-69. In some embodiments, the binding agent is a polypeptide such as an antibody comprising a light chain CDR1 amino acid sequence selected from the group consisting of SEQ ID NOS. 70-92. In some embodiments, the binding agent is a polypeptide such as an antibody comprising a heavy chain CDR2 amino acid sequence selected from the group consisting of SEQ ID NOS. 93-115. In some embodiments, the binding agent is a polypeptide such as an antibody comprising a heavy chain CDR3 amino acid sequence selected from the group consisting of 116-138. In some embodiments, the binding agent is a polypeptide such as an antibody comprising one or more of SEQ ID NOS. 170-176, 178-184, 186-193, and/or 195-202. In some embodiments, the binding agent is a polypeptide such as an antibody comprising one or more of SEQ ID NOS. 170-176 and one or more of SEQ ID NOS. 178-184. In some embodiments, the binding agent is a polypeptide such as an antibody comprising one or more of SEQ ID NOS. 186-193 and one or more of SEQ ID NOS. 195-202. In some embodiments, the binding agent comprises the combinations of CDRs shown in Tables 1A and/or 1B and/or has the properties described in any one or more of Tables 2 and/or Tables 5-7.

In some embodiments, the binding agent is derived from or related to (e.g., by sequence or derivation) a human antibody, human IgG, human IgG1, human IgG2, human IgG2a, human IgG2b, human IgG3, human IgG4, human IgM, human IgA, human IgA1, human IgA2, human IgD, human IgE, canine antibody, canine IgGA, canine IgGB, canine IgGC, canine IgGD, chicken antibody, chicken IgA, chicken IgD, chicken IgE, chicken IgG, chicken IgM, chicken IgY, goat antibody, goat IgG, mouse antibody, mouse IgG, pig antibody, and/or rat antibody, and/or a derivative thereof. In some embodiments, the derivative may be selected from the group consisting of an F_{ab}, F_{ab2}, Fab' single chain antibody, F_v, single chain, mono-specific antibody, bispecific antibody, trimeric antibody, multi-specific antibody, multivalent antibody, chimeric antibody, canine-human chimeric antibody, canine-mouse chimeric antibody, antibody comprising a canine Fc, humanized antibody, human antibody, caninized antibody, CDR-grafted antibody, shark antibody, nanobody, and/or canelid antibody. In some embodiments, the binding agent may be a humanized antibody comprising one or more of the amino acid sequence(s) (or be encoded by a nucleic acid sequence encoding such amino acid sequence(s)) of SEQ ID NOS. 170-176, 178-184, 186-193, and/or 194-202, and/or derivatives or variants thereof (e.g., conservatively substituted derivatives or variants thereof).

In some embodiments, the binding agent may be a humanized antibody comprising at least one of SEQ ID NOS. 170-176 and at least one of SEQ ID NOS. 178-184, and/or derivatives or variants thereof (e.g., conservatively substituted derivatives or variants thereof). In some embodiments, the binding agent exhibits approximately (i.e., within about 25%, about 20%, about 15%, or about 10% of; and/or a minimum 10 nM affinity (KD 10^{-8} M)) the binding affinities (ka (M^{-1}/s^{-1}), kd (s^{-1}), and KD (M)) for human and monkey PD-1 demonstrated by humanized antibody A35796 (comprising SEQ ID NOS. 170 and 178), humanized antibody A35793 (comprising SEQ ID NOS. 171 and 179), humanized antibody A35818 (comprising SEQ ID NOS. 172 and 180), humanized antibody A35795 (comprising SEQ ID NOS. 173 and 181), humanized antibody A35797 (comprising SEQ ID NOS. 174 and 182), humanized antibody A35799 (comprising SEQ ID NOS. 175 and 183), or humanized antibody A35805 (comprising SEQ ID NOS. 176 and 184), as shown in Table 6.

In other embodiments, the binding agent may be a humanized antibody comprising at least one of SEQ ID NOS. 186-193 and at least one of SEQ ID NOS. 195-202, and/or derivatives or variants thereof (e.g., conservatively substituted derivatives or variants thereof). In some embodiments, the binding agent exhibits approximately (i.e., within about 25%, about 20%, about 15%, or about 10% of; and/or a minimum 10 nM affinity (KD 10^{-8} M)) the binding affinities (ka (M^{-1}/s^{-1}), kd (s^{-1}), and KD (M)) for human and monkey PD-1 as humanized antibody A35775 (comprising SEQ ID NOS. 186 and 195), humanized antibody A35783 (comprising SEQ ID NOS. 187 and 196), humanized antibody A35774 (comprising SEQ ID NOS. 188 and 197), humanized antibody A36443 (comprising SEQ ID NOS. 189 and 198), humanized antibody A35777 (comprising SEQ ID NOS. 190 and 199), humanized antibody A35789 (comprising SEQ ID NOS. 191 and 200), humanized antibody A36448 (comprising SEQ ID NOS. 192 and 201), or humanized antibody A36437 (comprising SEQ ID NOS. 193 and 202), as shown in Table 7.

In some embodiments, the binding agent comprises at least a least a first and second specificity, the first being against PD-1 and the second being against a different antigen (e.g., an antigen of an infectious agent such as HIV (e.g., env) and/or a tumor antigen). In some embodiments, the binding agent and/or derivative thereof may comprise a detectable label fixably attached thereto. In some embodiments, the binding agent of any one and/or derivative thereof comprises an effector moiety (e.g., a cytotoxic drug, toxin, diphtheria A chain, exotoxin A chain, ricin A chain, abrin A chain, curcin, crotin, phenomycin, enomycin, and radiochemical) fixably attached thereto. In some embodiments, polynucleotides encoding one or more binding agents are also provided (e.g., as an expression vector). Host cells comprising and/or expressing the polypeptide products of such polynucleotides are also provided. In some embodiments, compositions comprising at least one binding agent or derivative; at least one isolated polynucleotide; at least one expression vector; and/or, at least one host cell; or a combination thereof; and, a pharmaceutically acceptable carrier are also provided.

This disclosure also provides methods for detecting PD-1 on a cell, the method comprising contacting a test biological sample with a binding agent or derivative described herein and detecting the binding agent bound to the biological sample or components thereof. Such methods may be an in vivo method or an in vitro method. In some embodiments, the method may comprise comparing the amount of binding to the test biological sample or components thereof to the amount of binding to a control biological sample or components thereof, wherein increased binding to the test biological sample or components thereof relative to the control biological sample or components thereof indicates the presence of a cell expressing PD-1 in the test biological sample

(e.g., mammalian blood). In some embodiments, a system for identifying a PD-1 antibody binding agent by assaying the candidate binding agent by the exhaustion functional recovery assay (EFRA); determining the affinity of the candidate binding agent for PD-1; and, determining the nucleotide sequence of the CDR of the candidate binding agent is provided.

In some embodiments, a kit for detecting the expression of PD-1 in or on a cell, the kit comprising a binding agent or derivative thereof and instructions for use. In some embodiments, the binding agent and/or derivative thereof is in lyophilized form.

In some embodiments, this disclosure provides methods for treating, preventing and/or ameliorating an infectious disease, cancer and/or autoimmunity in a mammal comprising administering to the mammal at least one effective dose of a pharmaceutical composition comprising a binding agent or derivative thereof. In some embodiments, the infectious disease is human immunodeficiency virus (HIV). In some embodiments, the binding agent and/or derivative thereof used to treat infectious disease and/or cancer is a PD-1 antagonist. In some embodiments, the binding agent and/or derivative thereof used to treat an autoimmune condition is a PD-1 agonist. In some embodiments, multiple doses are administered to the animal. In some embodiments, the binding agent and/or derivative thereof may be administered in a dosage amount of about 1 to 50 mg/kg.

This disclosure also provides combinations of PD-1 binding agents. In some embodiments, the combination comprises a first binding agent that blocks the interaction of PD-1 and PD-L1 and a second binding agent that does not block the interaction of PD-1 and PD-L1. Exemplary combinations may include, for instance, one or more of the competitive anti-PD-1 antibodies and one or more of the non-competitive binding agents described herein, such as any one or more of those comprising the amino acid sequences of 135C12 (SEQ ID NOS. 17, 40, 63, 86, 109, and 132), 139D6 (SEQ ID NOS. 2, 25, 48, 71, 94, and 117), 135D1 (SEQ ID NOS. 3, 26, 49, 72, 95, and 118), and/or 136B4 (SEQ ID NOS. 19, 42, 65, 88, 111, and 134). Exemplary embodiments include the combination of competitive antibody MK3475 (Pembrolizumab) or a competitive binding agent comprising the amino acid sequences SEQ ID NOS. 8, 31, 54, 77, 100, and 123 (137F2) with a non-competitive PD-1 binding agent comprising the amino acid sequences (SEQ ID NOS. 17, 40, 63, 86, 109, and 132 (135C12). As illustrated in FIG. **15**, both of these exemplary combinations results in an enhanced relief of functional exhaustion and increased proliferation of HIV-specific $CD8^+$ T cells beyond what either antibody alone can achieve. Other exemplary non-competitive antibodies that may be useful in combination with the competitive antibodies MK3475 or 137F2 and the non-competitive P2 patch-specific (M4 (FIG. **10**A, B)) binding agent 135D1 (comprising SEQ ID NOS. 3, 26, 49, 72, 95, and 118), and/or the non-competitive P2 patch-specific (M17 (FIG. **10**A, E)) binding agent 136B4 (comprising SEQ ID NOS. 19, 42, 65, 88, 111, and 134). Other combinations may also be suitable as may be determined by those of ordinary skill in the art.

Such combinations may be used for any use described herein or as may be otherwise ascertained by those of ordinary skill in the art. For instance, such combinations may be used in the methods for treating, preventing and/or ameliorating an infectious disease, cancer and/or autoimmunity in a mammal described herein. In some embodiments, methods for treating inflammation in a subject comprising administering a combination of at least two antagonistic PD-1 binding agents, wherein each of said binding agents having specificity for different epitopes on PD-1, at least one of said binding agents being competitive with the interaction of PD-1 and PD-L1, and at least one of said binding agents is non-competitive with the interaction of PD-1 and PD-L1 are also provided. This disclosure also provides methods for treating a chronic neurogenerative condition in a subject by administering a combination of at least two antagonistic PD-1 binding agents, wherein each of said binding agents having specificity for different epitopes on PD-1, at least one of said binding agents being competitive with the interaction of PD-1 and PD-L1, and at least one of said binding agents is non-competitive with the interaction of PD-1 and PD-L1. In some embodiments, the chronic neurogenerative condition is Alzheimer's disease. In some embodiments, multiple doses are administered to the mammal which may be separated by about a week, about two weeks, about three weeks, or preferably about a month, or longer.

This disclosure also provides methods for producing the binding agents described herein by expressing the binding agent in a cell and isolating the binding agent from the cell or a culture supernatant of the cell. In some embodiments, such methods may further comprise expressing a nucleic acid encoding such binding agent(s). In some embodiments, such methods may also include combining the binding agent(s) following isolation with one or more pharmaceutically acceptable excipients.

Methods for producing a combination(s) of binding agents, such as a first binding agent that blocks the interaction of PD-1 and PD-L1 and a second binding agent that does not block the interaction of PD-1 and PD-L1, are also provided by this disclosure. In some embodiments, the second binding agent binds PD-1. In some embodiments, the first and/or second binding agents are antibodies such monoclonal antibodies or fragments or derivatives thereof. In some embodiments, the second binding agent comprises the amino acid sequences SEQ ID NOS. 17, 40, 63, 86, 109, and 132 (e.g., 135C12); SEQ ID NOS. 2, 25, 48, 71, 94 and 117 (e.g., 139D6); SEQ ID NOS. 3, 26, 49, 72, 95, and 118 (e.g., 135D1); and/or SEQ ID NOS. 19, 42, 65, 88, 111, and 134 (e.g.,136B4). In some embodiments, these methods may further include the addition of a pharmaceutically acceptable excipient.

The terms "about", "approximately", and the like, when preceding a list of numerical values or range, refer to each individual value in the list or range independently as if each individual value in the list or range was immediately preceded by that term. The terms mean that the values to which the same refer are exactly, close to, or similar thereto.

As used herein, a subject or a host is meant to be an individual. The subject can include domesticated animals, such as cats and dogs, livestock (e.g., cattle, horses, pigs, sheep, and goats), laboratory animals (e.g., mice, rabbits, rats, guinea pigs) and birds. In one aspect, the subject is a mammal such as a primate or a human.

Optional or optionally means that the subsequently described event or circumstance can or cannot occur, and that the description includes instances where the event or circumstance occurs and instances where it does not. For example, the phrase optionally the composition can comprise a combination means that the composition may comprise a combination of different molecules or may not include a combination such that the description includes both the combination and the absence of the combination (i.e., individual members of the combination).

Ranges may be expressed herein as from about one particular value, and/or to about another particular value.

When such a range is expressed, another aspect includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent about or approximately, it will be understood that the particular value forms another aspect. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint. Ranges (e.g., 90-100%) are meant to include the range per se as well as each independent value within the range as if each value was individually listed.

The term "combined" or "in combination" or "in conjunction" may refer to a physical combination of agents that are administered together or the use of two or more agents in a regimen (e.g., administered separately, physically and/or in time) for treating, preventing and/or ameliorating a particular disease.

When the terms treat, prevent, and/or ameliorate or derivatives thereof are used herein in connection with a given treatment for a given condition (e.g., preventing cancer or infection by HIV), it is meant to convey that the treated patient either does not develop a clinically observable level of the condition at all, or develops it more slowly and/or to a lesser degree than he/she would have absent the treatment. These terms are not limited solely to a situation in which the patient experiences no aspect of the condition whatsoever. For example, a treatment will be said to have prevented the condition if it is given during exposure of a patient to a stimulus that would have been expected to produce a given manifestation of the condition, and results in the patient's experiencing fewer and/or milder symptoms of the condition than otherwise expected. For instance, a treatment can "prevent" infection by resulting in the patient's displaying only mild overt symptoms of the infection; it does not imply that there must have been no penetration of any cell by the infecting microorganism.

Similarly, reduce, reducing, and reduction as used herein in connection with prevention, treatment and/or amelioration of a given condition by a particular treatment typically refers to a subject developing an infection more slowly or to a lesser degree as compared to a control or basal level of developing an infection in the absence of a treatment (e.g., administration of one or more PD-1 binding agents). A reduction in the risk of infection may result in the patient's displaying only mild overt symptoms of the infection or delayed symptoms of infection; it does not imply that there must have been no penetration of any cell by the infecting microorganism.

All references cited within this disclosure are hereby incorporated by reference in their entirety. Certain embodiments are further described in the following examples. These embodiments are provided as examples only and are not intended to limit the scope of the claims in any way.

EXAMPLES

Example 1

Generation and Characterization of PD-1 Binding Agents

Four mice strains (total of 16 mice) have been immunized with two PD-1 proteins, i.e. human PD-1 Fc fusion protein and a human PD-1 monomeric protein. Mice showing serum reactivity to PD-1 expressed on activated human T lymphocytes have been selected for generation of anti-PD-1 hybridoma cell lines. A total of 240 PD-1 hybridoma cell lines were selected for producing antibodies that bind to recombinant PD-1 protein. The primary criteria for the first round of antibodies selection were: i) staining of PD-1 on activated human T lymphocytes by flow cytometry; ii) diversity of CDR VH and VL sequences as compared to those of the existing anti-PD-1 antibodies; and, iii) epitope mapping performed by competitive binding studies with PD-1 conjugated Luminex beads with two commercially available anti-PD-1 antibodies binding to different epitopes on PD-1. A second round of selection was then carried out by: iv) affinity binding assays (not a primary criteria as it does not correlate with the stimulatory potential of anti-PD-1 antibodies); v) evaluation of anti-PD-1 antibodies that bind PD-1 and are either competitive, partially competitive or non-competitive with the binding of PD-L1 in a Luminex biochemical assay; and, vi) functional characterization of antibodies as agonist (not able to restore T-cells from functional exhaustion) or antagonist (able to restore T-cells from functional exhaustion). In these studies, the antibodies were tested and differentiated based on their ability to rescue proliferation in HIV-specific exhausted CD8 T-cells.

In a primary screen of antibody supernatants from individual cell cultured hybridoma cell clones, the EFRA assay was carried out to evaluate the functional effect of anti-PD1 antibodies on the proliferation of HIV-specific CD8 T cells (FIG. **2**). Antibody clones in the upper box (E8-3, C2-3, E1-3, F3-3, H8-3, C10-2, G2-1, G3-2, H2-1, and H4-2) act as PD-1 antagonists and stimulate proliferation while antibody clones in the lower box (C8-1 and G10-2) are agonistic and promote the PD-1 negative regulatory effect. The level of proliferation induced by the peptide control (Pep 8) is indicated by the lower horizontal line (just below 1%) and the induced proliferation by the Merck MK-3475 anti-PD1 antibody is shown in the upper horizontal line (just above 2%). Antibodies of interest identified by these processes underwent a second round of subcloning and the resulting hybridoma clones were used for the production and purification of the antibodies in Table 2. Binding assays were carried out with the purified anti-PD-1 antibodies to ensure that the subclones retained their affinity for PD-1. The concentration response binding of anti-PD-1 antibodies to cell surface PD-1 was evaluated on activated CD4 T-cells (FIG. **3**).

The EFRA provides for the selection of binding agents that restore T-cells from functional exhaustion but are not necessarily antagonistic, meaning those binding agents that do not necessarily interfere with the interaction between PD-1 and its biological ligand(s) (e.g., PD-L1 or PD-L2). An embodiment of the EFRA was to identify such binding agents (antibodies) that bind PD-1. Epitope mapping of antibody binding to PD-1 was performed with two seperate biochemical assays. In one assay, competitive binding to PD-1 Fc fusion protein labeled beads was evaluated between one of two commercial anti-PD-1 antibodies (clones EH12.2H7 and J116) and the anti-PD-1 antibodies listed (also described in Table 2). Four classes of monoclonal antibodies binding to distinct epitopes were identified based on this assay. These are: class 1 (competitive with the EH12.2H7 commercial monoclonal antibody clone that blocks the interaction of PD-1 with PD-L1), class 2 (competitive with the J116 commercial monoclonal antibody clone that binds PD-1 but does not effectively block the interaction of PD-1 with PD-L1), class 3 (competitive with both the EH12.2H7 and J116 commercial monoclonal antibodies), and class 4 (non-competitive with either the EH12.2H7 or J116 commercial antibodies). Antibodies were binned into one of the four binding classes and the relative

binding of these antibodies for cell surface PD-1 is represented by the mean fluorescence intensity (MFI) relative to a control anti-PD-1 antibody in FIG. **4**. These results show that tight binding antibodies were identified from all four binding classes. A second Luminex binding assay was used to directly evaluate if an anti-PD-1 antibody blocks the interaction between PD-1 and PD-L1. This assay was carried out using PD-1 Fc fusion protein coated beads that were incubated in the absence or presence of different concentrations of the anti-PD-1 antibodies listed in Table 2. A fixed concentration of biotinylated PD-L1, approximately equivalent to the IC_{50} of the PD-1/PD-L1 interaction, was then incubated with the PD-1/antibody complex and PD-L1 binding was detected using fluorescently labeled streptavidin (representative binding curves shown in FIG. **5***a-c*). Using this biochemical assay, antibodies were defined as being competitive, partially competitive or non-competitive with the PD-1/PD-L1 interaction. The competitive, partially competitive and non-competitive antibodies were identified which bind distinct sites on PD-1 and exhibit high binding affinity (Table 2). Further evaluation of antibodies that bind PD-1 and are non-competitive or partially competitive with PD-L1 were performed by incubating PD-1 Fc fusion protein coated Luminex beads with 20 nM of an anti-PD-1 antibody from Table 2 followed by an incubation of the PD-1/antibody complex with different concentrations of biotinylated PD-L1. FIG. **5***d-f* shows that a competive anti-PD-1 antibody competely blocks the interaction between PD-1 and PD-L1. Partially competitive and non-competitive anti-PD-1 antibodies listed in Table 2 results in a shift in the binding affinity of PD-L1 for PD-1, but does not block the interaction when concentration of PD-L1 are increased. Some of these antibodies were also shown to exhibit statistically significant increases in proliferation relative to controls (peptide 8 alone control or the peptide and IgG1 isotype control antibody in FIGS. **6***a* and **6***b*). Class 1 antibodies (competitive with the EH12.2H7 commercial monoclonal antibody that blocks the interaction of PD-1 with PD-L1) or competitive in the PD-1/PD-L1 intereaction assay were generally determined to provide improved proliferative restoration. In combining the data from multiple EFRA experiments and using MK-3475 as the common comparator, FIG. **7** shows that select antibodies described in Table 2 exhibited equivalent or statistically improved activity ($p<0.007$) compared to the benchmark MK-3475 antibody.

Example 2

Antibody Combinations

Combinations of antibodies binding to different PD-1 epitopes were found to enhance restoration of HIV peptide specific CD8 T-cell proliferation in a functional exhaustion recovery assay (FIG. **8**). Synergy between antibody types was also observed. For instance, it was determined that class 1 (MK-3475 in FIG. **8**) and class 2 (139D6 in FIG. **8**) antibodies are able to simultaneously bind PD-1. While the maximum stimulation observed for MK-3475 is consistently about 200% relative to the HIV peptide, combinations of MK-3475 and 139D6 monoclonal antibodies at 5 μg/ml exhibited synergy with a 288% increase in HIV-specific CD8 T cell proliferation relative to the HIV peptide control alone or a 144% increased proliferation relative to MK-3475 or 139D6 added alone (FIG. **8**). This synergistic increase in proliferation was observed in several experimental tests with a statistically significant p value of 0.007. As a comparison, addition of 10 μg/ml of either MK-3475 or 139D6 alone did not result in an increased proliferation in the EFRA. Thus, the combination of a first binding agent that blocks the interaction of PD-1 and PD-L1 with a second binding agent that does not block the interaction of PD-1 and PD-L1 has been determined to act synergistically to rescue T cells from exhaustion.

Example 3

Epitope Mapping of Anti-PD-1 Antibodies

Preliminary epitope mapping evaluations relied on biochemical competitive binding assay studies between commercially available anti-PD-1 antibodies (EH12.2H3 and J116) and the newly identified anti-PD-1 antibodies defined in this patent. This procedure allowed us to categorize the antibodies into one of four binding classes based on binding competitively or non-competitively with either of the two commercial antibodies. A more precise method of defining the antibody binding epitopes on PD-1 is to monitor the interaction of the antibody with different PD-1 proteins that have discreet amino acid substitutions at solvent accessible residues. If these residues are important for tight binding of the anti-PD-1 antibodies, the substitution can result in a reduced binding for the PD-1 protein. These studies were performed by site directed mutagenesis of the PD-1 gene encoded within the pReceiver-M67 mammalian expression vector under the control of CMV promoter. Using the 3RRQ PDB published structural data for the PD-1 protein, 31 different PD-1 clones were designed with single, double or triple amino acid substitutions at solvent accessible residues. The residues implicated in the interaction between PD-1 and PD-L1/L2 were determined based on the published crystal structure of the complex between human PD-1 and PD-L2 (Lazar-Molnar, PNAS, 2008, p10483-10488) and mapped to the PD-1 structure in FIG. **9** as purple spheres. Substitutions were selected at residues that are implicated in the PD-1/PD-L1 interaction (represented by M10, M11, M12, M14, M23, M24, M25), or on opposite or adjacent surfaces of the PD-1 protein not implicated in the PD-L1 interaction (represented by M1, M2, M3, M4, M5, M6, M7, M8, M9, M13, M15, M16, M17, M18, M19, M20, M21, M22, M26, M27, M28, M29, M30, M31) and are defined in FIG. **10**. The PD-1 encoding DNA vectors were then used to transiently transfect HeLa cells using the Lipofectamine 2000 transfection reagent. Cells were incubated in a cell culture incubator at 37° C. for 36-48 hours to allow for cell surface expression of the PD-1 protein, and then cells were re-suspended and incubated for 30 minutes with between 0.3 to 2 μg/ml of a given anti-PD-1 antibody selected from Table 2. Following a wash step, cells were stained with a PE labeled anti-mouse IgG secondary antibody then analyzed by flow cytometry. In each experiment, the wild type PD-1 protein was used as a positive control for antibody binding and several antibodies binding different epitopes on PD-1 (as determine by being competitive or non-competitive with the PD-1/PD-L1 interaction or from competitive binding studies with commercially available PD-1 clones) were evaluated in parallel to monitor the relative expression level of the PD-1 protein with the different amino acid substitutions. All anti-PD-1 antibodies tested from Table 2 bound specifically to HeLa cells transfected with wild type PD-1 but not to cells that were transfected with an empty vector control. All mutant PD-1 proteins expressed at near wild type levels or gave a significant shift in mean fluorescence intensity relative to an untransfected contol when stained with anti-PD-1 antibodies

that were either competitive or non-competitive with the PD-1/PD-L1 interaction. A select set of antibodies from Table 2 were then systematically tested for their ability to bind either wild type or mutant PD-1 protein expressed at the cell surface of the transfected HeLa cells. These results are summarized in Table 5 with the mutations indicated that abrogate or reduce binding for each of the different anti-PD-1 antibody clones. Flow cytometry histograms depicted in FIG. **11** to FIG. **14** give examples of different antibodies that either bind effectively or with reduced affinity to HeLa cells transfected with the indicated mutant PD-1 constructs. As predicted, antibodies that were shown to be competitive with the PD-1/PD-L1 interaction in a biochemical assay (MK-3475, 137F2, 140G5, and 139F11) also bound to epitopes on PD-1 at this interaction site. Consistent with the biochemical PD-1/PD-L1 interaction studies, antibodies that were non-competitive with the PD-1/PD-L1 interaction (136B4, 135C12, 136E10) bound to distinct epitopes that were distal to amino acid residues implicated in the PD-1/PD-L1 interaction.

TABLE 5

Epitope mapping of the different anti-PD-1 antibody clones that are either competitive or non-competitive with the PD-1/PD-L1 interaction.

Clone	Affinity* (nM)	Binding Class**	Antibody competition with the PD-1/PD-L1 interaction***	EFRA % relative to peptide alone‡	PD-1 mutation that induces a reduced affinity
137F2	1.5	1	Competitive	250%	M23
139F11	3.1	1	Competitive	250%	M23
140G5	1.6	1	Competitive	205%	M15
135C12	1.7	2	Partial competition	195%	M4, M17§, M18§, M28§, M31§
139D6	2.4	2	Partial competition	195%	M4
135D1	6.5	2	Partial competition	187%	M4
136B4	1.4	2	Non-competitive	185%	M17, M18
140A1	1.4	3	Competitive	160%	M13
122F10	2.2	4	Non-competitive	146%	M17
134D2	4.8	4	Competitive	205%	M13, M15, M17§
136E10	7.1	4	Non-competitive	148%	M1
MK3575	0.6	1	Competitive	198%	M13, M14

*Binding affinity for the antibodies listed in Table 1 was evaluated by FACS staining of endogenous cell surface PD-1 on activated CD4 T cells.

**Binding class was determined by Luminex assay competitive binding studies. Binding class 1 mAb clones are competitive with the EH12.2H7 clone commercial antibody, class 2 mAb clones are competitive with the J116 clone commercial antibody, class 3 mAb clones are competitive with both EH12.2H7 and J116 antibodies and class 4 mAb clones bind in the presence of both EH12.2H7 and J116 antibodies.

***Antibody competition with the PD-1/PD-L1 interaction was determined in a second Luminex binding assay. In this assays, PD-1 Fc fusion protein coated beads were incubated in the absence or presence of an anti-PD-1 antibody from Table 2 at a concentration of 20 nM. A fixed concentration of 1.25 nM biotinylated PD-L1, approximately equivalent to the IC_{50} of the PD-1/PD-L1 interaction, was then incubated with the PD-1/antibody complex and PD-L1 binding was detected by fluorescence with phycoerythrin labeled streptavidin. Based on PD-L1 binding to the PD-1/antibody complex, antibodies were defined as being competitive, partially competitive or non-competitive with the PD-1/PD-L1 interaction.

‡Proliferative effect is evaluated using a CFSE assay (an embodiment of the Exhaustion Functional Recovery Assay, "EFRA"). PBMCs isolated from a chronically infected HIV subject were stimulated with an HIV specific peptide in the presence and absence of an anti-PD-1 antibody. Following a 6 day incubation, proliferation of HIV specific CD8 T cells was evaluated in the anti-PD-1 treated samples relative to the peptide alone control.

§Small shift in antibody binding to mutant PD-1 encoding amino acid substitutions.

NA = not available

Example 4

Non-Blocking Antibody Epitope Connected with a Novel Antagonistic Action of PD-1

Antibodies binding to diverse epitopes on PD-1 were evaluated for their antagonistic activity in a functional exhaustion recovery assay. These studies revealed antagonistic antibodies could be either competitive or non-competitive with the PD-1/PD-L1 interaction. Considering that the mode of action attributed to functional activity of anti-PD-1 antibodies is through PD-1 blockade, these results point to a novel function of PD-1 that is being inhibited by the non-competitive antagonistic antibodies. This assertion is supported by the fact that the combination of competitive and non-competitive anti-PD-1 antibodies leads to an enhanced antagonistic activity in the in vitro exhaustion functional recovery assay. This enhanced functional activity is beyond the level of induction that can be reached with either antibody when administered alone and was demonstrated with different combination of competitive anti-PD-1 antibodies (MK3475 or 137F2) with the non-competitive anti-PD-1 antibody 135C12 (FIG. **15**). As a further proof of their functional activity, anti-PD-1 antibodies were tested either alone or in combinations between PD-1/PD-L1 competitive and non-competitive antagonistic antibodies in a mixed lymphocyte reaction assay (MLR). The MLR assay involved the mixing of monocytes from one healthy donor with the PD-1+ memory CD4 T cells from a second healthy donor. Monocytes were isolated from peripheral blood mononuclear cells (PBMCs) by CD14 positive selection with magnetic beads. PBMCs from a second donor were first depleted of CD45RA expressing cells with magnetic beads then a different set of magnetic beads were used for positive selection for CD4 positive T cells. These memory CD4 T cells (CD4+ CD45RA−) were then stained with an Aqua Live/Dead staining kit and the 127C2 anti-PD-1 antibody clone (shown to have no antagonistic activity and to not compete with MK3475, 137F2 or 135C12 for binding to PD-1) and a secondary anti-Mouse PE antibody in order to sort on the viable PD-1+ cell population. After mixing monocytes and CD4 T cells from the two different donors at 1:2 or 1:5 ratios, cells were either left untreated or treated with 1 μg/ml of the anti-PD-1 antibodies indicated in FIGS. **16***a* and **16***b*. Following 5 days in a cell culture incubator, aliquots of cell culture supernatants were collected and

analyzed for secreted IFNγ by ELISA. Tritiated thymidine (^{3}H-TdR) was added to the cell culture medium and the cells were incubated for a further 18 hours. ^{3}H-TdR incorporation was used as a measure of cellular proliferation. This second independent in vitro assay confirmed the functional activity of our anti-PD-1 antibodies. In FIG. **16***a*, we see an increased proliferation of up to 2-fold for CD4 T cells induced by individual and combinations of anti-PD-1 antibodies. In FIG. **16***b*, we see a strong increase in IFNγ production for all anti-PD-1 antibodies when tested individually with 137F2 giving the highest levels of induction. In combinations of competitive and non-competitive anti-PD-1 antibodies (either MK3475 and 135C12 or 137F2 and 135C12), we see a trend towards an increased proliferation and increased production of IFNγ from PD-1+ memory CD4 T cells. Given that increased IFNγ production from CD4$^+$ T cells is associated with reduced pathology and improved memory in a mouse model for Alzheimer's disease when treated with a PD-1 immune checkpoint blockade therapy (Baruch K, Nature Med, 2015), treatment with anti-PD-1 antibodies or combinations of anti-PD-1 antibodies as outlined within, would be expected to have an equivalent or improved therapeutic benefit. As described below, epitope mapping revealed that the non-competitive antibodies with the greatest potency all bind to a similar patch of PD-1, referred to herein as the "P2 patch", that overlaps with the region of the M4 amino acid substitutions (serine38 to alanine, proline39 to alanine and leucine41 to alanine (FIG. **10**; SEQ ID NO. 142)), and/or the region of the M17 amino acid substitutions (asparagine 102 to alanine and arginine 104 to leucine (FIG. **10**; SEQ ID NO. 155)), and/or the region of the M18 amino acid substitutions (aspartate 105 to alanine (FIG. **10**; SEQ ID NO. 156), and/or the region of the M31 amino acid substitutions (leucine 41 to alanine and valine 43 to leucine (FIG. **10**; SEQ ID NO. 206).

To further investigate the regions of PD-1 that are implicated in the antagonistic activity of the anti-PD-1 antibodies, solvent accessible variant amino acid residue from different species were mapped to the human PD-1 structure. This structural representation based on the 3RRQ PDB shows the face of PD-1 that interacts with PD-L1/L2 in FIG. **17***a* and the opposite side of PD-1 in FIG. **17***b*. The residues that are dissimilar between monkey and human PD-1 are indicated by red circles, other variant residues found in rodent PD-1 (mouse and rat) are displayed as green circles and additional variant residues from dog PD-1 are shown in orange. Residues 46, 58, 74 and 116 have been implicated as sites from N-linked glycosylation and are marked by cyan circles. Alignments of human, monkey, horse, dog, mouse and rat PD-1 ectodomain amino acid sequences are shown in FIG. **17***c* and the corresponding homologies with human PD-1 are 96.6%, 79.9%, 73.2%, 62.4% and 66.4%, respectively. With these cross-species variant residues of PD-1 displayed on the structure, it becomes evident that there are two conserved patches on PD-1 that are designated P1 and P2 in FIGS. **17***a* and **17***b*. The P1 patch corresponds to the central region involved in the interaction between PD-1 and the PD-L1/PD-L2 ligands (compare the residues marked with purple circles in FIG. **9** with the circles shown in FIG. **17***a*). Cross-species conservation of this P1 patch is anticipated since variant residues that accumulate in PD-1 during evolution would still need to maintain the interaction with the PD-L1/L2 ligands. Select substitutions of residues implicated in the PD-1/PD-L1 interaction are observed with mouse variants (e.g. residues 64 and 68) and could be attributed to co-evolution of PD-1 with its PD-L1/L2 ligands however; the core interaction region within P1 remains conserved. The evolutionarily conserved P2 patch occupies a similar surface area to the P1 patch and yet, this region has no previously identified role for PD-1, either structurally or functionally. The fact that the P2 patch is evolutionarily conserved in the species investigated indicates that PD-1 was under functional pressure to preserve the P2 site. This conservation is all the more significant given that the PD-1 ectodomain is only 62.4% to 79.9% conserved in four of the species investigated. Taking into account all the variant residues across these four species compared to human PD-1 give an even lower 52.3% sequence conservation (FIG. **17***c*, blue arrows represent the structural region depicted in FIGS. **17***a* and **17***b*). Whether this functional pressure is attributed to the P2 patch serving as an interaction site for an as yet unidentified ligand, site for higher order complex formation or linked with PD-1 related signaling events remains to be determines. However, anti-PD-1 antibodies described in this patent including 135C12, 139D6, 135D1 and 136B4 that have overlapping binding epitopes with P2 patch provide direct evidence for the functional importance of this region.

Given that this region has no previous implication in the functional activity of PD-1, it is proposed herein that antibodies exemplified by 135C12 and binding to Patch 2 on PD-1 shown in FIG. **17***b* represent a novel mechanism and site to exert an antagonistic activity on PD-1. It is further proposed herein that other antibodies, antibody fragments, or other protein binding agents that can interact with this Patch 2 region of PD-1 would also act as an antagonist of PD-1 in a manner that is distinct from and complementary to anti-PD-1 antibodies that act through blockade of the PD-1/PD-L1 interaction as demonstrated in FIGS. **8**, **15** and **16**.

Example 5

Antibody Competitive Binding Studies

To further characterize the binding epitopes of select antibodies listed in Table 2, a series of antibody competition studies were performed for binding to cell surface PD-1. Antibodies binding to distinct epitopes on PD-1 (MK3475, 137F2, 135C12 and 134D2) were chemically conjugated using a Maxpar antibody labeling kit (Fluidigm). In this procedure, the antibody disulfide bonds are partially reduced in order to conjugate cysteine residues with a metal chelating polymer. These metal isotope modified antibodies were then be used to stain cell for the expression levels of surface PD-1 with the analysis performed by mass cytometry. In order to generate CD4 cells with high expression levels of PD-1, peripheral blood mononuclear cells from a health donor were stimulated with PHA and IL-2 and incubated for 5 days. Following cell staining, gating was performed to select viable, CD3+/CD4+ cells and cell surface levels of PD-1 were evaluated for each sample by mass cytometry. In the antibody competition assay, samples of 2×10^6 cells were incubated for 30 minutes at 4° C. with 15 μg/ml of one of the indicated competitor antibodies indicated in FIG. **18**. One of the staining anti-PD-1 antibodies labeled with a metal isotope (MK3475, 137F2, 135C12, or 134D2) was then added to the cells at <1 μg/ml, incubated for a further 20 minutes then washed to remove unbound antibody and analyzed for the levels of cell surface PD-1. A mouse IgG1 isotype control antibody was used as a negative control and as a reference to calculate the percent PD-1 positive cells relative to samples incubated with the anti-PD-1 competitor antibody clones.

The Class 1 anti-PD-1 antibodies that are competitive with the PD-1/PD-L1 interaction are all competitive (indicated as a red box in FIG. **18** with <29% staining of PD-1 positive cells relative to the IgG1 control) in experiments were PD-1 high cells were stained with either MK3475 or 137F2. These results are expected given that epitope mapping for several of these antibodies have binding sites that are either identical or overlapping. Class 1 antibodies were also competitive or partially competitive (yellow box in FIG. **18** with 30-59% staining relative to the IgG1 control) with the 134D2 antibody. Although competitive with the PD-1/PD-L1 interaction, 134D2 binds to an epitope that is overlaps primarily with the M15 mutant but also to a lesser extent with the 17 mutation. Class 1 antibodies were found to be non-competitive with the 135C12 antibody confirming the epitope binding studies that show that these antibodies bind distinct sites on PD-1.

Using Class 2 antibodies as the competitors, both MK3475 and 137F2 labeled antibodies bind with little to no reduction in binding relative to the IgG1 control. The one exception is the 135D1 antibody that blocked the PD-1 binding of labeled 137F2. Given that the 135D1 epitope is near the M4 mutation, it seems likely that there is some stearic hingerance in the 137F2 antibody binding in the region of the M23 mutation region. The 135C12 and 139D6 clones also have a shift in binding to PD-1 encoding the M4 mutation, however given that they do not compete with the binding of 137F2, these class 2 antibodies bind closer to the P2 patch. The 135C12 antibody also had small shifts in binding to M17, M18, M28, and M31 mutations which are all found at the edge of the P2 patch. All Class 2 antibodies used as competitors block the binding of labeled 135C12 which confirms that they are binding to binding to overlapping epitopes on PD-1. Most Class 2 competitor antibodies do not compete with labeled 134D2 for binding to PD-1. The 136B4 antibody is an exception for the class 2 antibodies that blocks the binding of 134D2. These results are consistent with the epitope binding studies in Example 1 where 134D2 binding to PD-1 is partially disrupted by the M17 mutation but primarily by the M13 and M15 mutations. Binding of the 136B4 antibody is only disrupted by the M17 and M18 mutations that is on the edge or within the P2 patch.

The Class 3 antibodies are competitive to partially competitive with MK3475 and 137F2 and bind PD-1 non-competitively with 135C12. The 135E10 class 3 antibody is competitive with labeled 134D2 while the 140A1 class 3 antibody is non-competitive with labeled 134D2. Epitope mapping shows that 140A1 binds in the region of the M13 mutation which is distinct from the binding epitope for 134D2 (M15 major and M17 minor).

In evaluating the functional data for the Class 4 antibodies, only 134D2 and 136B5 have significant antagonistic activity that leads to an increased proliferation of HIV specific CD8 T cells in the exhaustion functional recovery assay (>150% increased proliferation as indicated in FIG. **18**). These antibodies also block the interaction of PD-1 with PD-L1 in a biochemical assay and hence mostly likely function as antagonists through PD-1/PD-L1 blockade. Since excess 136B5 blocks the staining of PD-1+ cells with labeled 134D2, these antibodies bind PD-1 at similar or overlapping epitopes (FIG. **18**). The competitive binding data with the remaining class 4 antibodies show that they bind to diverse sites on PD-1 and that this binding is generally non-overlapping with the 135C12 antibody. The 122F10 antibody is an exception which binds an analogous or overlapping epitope to 136B4 since these two antibodies have a similar binding profile in the antibody competition studies (FIG. **18**) and both have reduced binding to the M17 mutant PD-1 construct (Table 5).

In combining the information from the epitope mapping studies performed by amino acid substitutions at solvent accessible residues of PD-1 (Example 1) and the antibody competition studies (FIG. **18**), we can generate a consistent structural map of the regions on PD-1 that are bound by the different anti-PD-1 antibody clones (FIGS. **19***a* and **19***b*). These binding epitopes are indicated with different colored circular patches for each of the clones in Table 5. FIG. **19***a* shows the face of PD-1 that has the majority of the residues involved in the PD-1/PD-L1 or PD-1/PD-L2 interactions. The exceptions are residues 89 and 90 that are found on the left side of FIG. **19***a* on a flexible loop region. The primary set of antibodies that are competitive with the PD-1/PD-L1 interaction all bind to this face of PD-1 including clones 137F2, 139F11, 140A1, 140G5 and MK3475. It should be noted that the two antibodies that we identified with the highest antagonistic activity in our functional assay (Table 5) both bind to the center of the P1 patch that is shown in FIG. **17***a* and centered on residues 124-126 of PD-1. This finding is confirmed by the fact that 137F2 and 139F11 have significantly different heavy and light chain CDR sequences and belong to distinct families based on sequence alignments of all the antibody clones discussed in this application.

Antibody clones 134D2 and 136B5 were shown to be competitive with the PD-1/PD-L1 interaction in a biochemical assay although they bind to a region of PD-1 in FIG. **19***b* that is overlapping with the M15 and M17 mutations. Based on this mapped epitope, these antibodies may be partially overlapping with residues PD-1 89 and 90 involved in the interaction with PD-L1 but may also induce a conformational change in PD-1 that inhibits binding to PD-L1. Consistent with these observations, antibody competition studies show that addition of a competitor Class 1 antibodies results in a significantly reduced binding of the labeled 134D2 antibody (FIG. **18**).

Antibodies that are non-competitive with the PD-1/PD-L1 interaction listed in Table 5 all bind to epitopes that are distant from residues involved in the PD-1/PD-L1 interaction. Antibodies that have strong functional activity all bind in epitopes that are overlapping with the P2 patch illustrated in FIG. **17***b*. The 135C12, 139D6 and 135D1 antibody clones have related heavy and light chain CDR sequences and bind to a site that overlaps with the M4, M18 and M31 mutations. The 135C12 antibody also binds competitively with the 136B4 clone but not with either the 134D2 or 136E10 clone. These antibody competitive binding studies further supports the binding of 135C12, 139D6 and 135C1 to an epitope that overlaps with the P2 patch. The binding epitope for the 136E10 antibody is localized by the M1 mutations which completely abrogates binding of this antibody to PD-1.

Example 6

Targeted Cell Killing through Antibody Drug Conjugates

As discussed herein, the binding agents such as antibodies (e.g., Table 2) may be conjugated with a toxin in order to perform a targeted killing of PD-1 expressing cells. An example of the therapeutic benefits of this strategy would include the targeted elimination of HIV-infected $CD4^+$ T-cells that are predominantly PD-1 positive. To perform

these studies, two different anti-PD-1 antibodies (140G5 and 136B5) were chemically conjugated with PEG4-vc-PAB-PNU-159682 (referred to as PNU from this point forward) through accessible cysteine groups following partial reduction of the antibody disulfide bonds. The antibody drug conjugates (ADC) were profiled by hydrophobic interaction chromatography and size exclusion chromatography, and both samples found to contain >95% PNU conjugated antibody. In the ADC killing assay, $CD4^+$ T cells were isolated from the PBMCs of a patient that was chronically infected with the HIV-1 virus. These $CD4^+$ T cells were incubated with an isotype control antibody, 140G5 mAb, 140G5-PNU mAb conjugate, 136B5 mAb, or 136B5-PNU mAb conjugate. Antibody concentrations were all at 10 μg/ml and cells were incubated at 37° C. in a cell culture incubator with 5% CO_2 for 5 days. On the fifth day, cells were stained for flow cytometry analysis with antibodies for monitoring cell surface levels of CD4 and PD-1 along with Aqua staining for cell viability and Annexin V staining to identify cells undergoing apoptosis. As shown in FIG. **20**, all samples treated with the different antibodies or ADCs have equivalent levels of Annexin V positive (FIG. **20***a*) or Aqua positive (FIG. **20***b*) $CD4^{30}$ T-cells that possess low- to mid-level expression of PD-1. However, in cell populations with high levels of PD-1, there is a significant increase in the amount of Annexin V and Aqua positive cells in samples treated with the anti-PD-1 ADCs (140G5-PNU and 136B5-PNU in FIGS. **20***a* and *b*).

To provide further evidence for the potential therapeutic benefit of an anti-PD-1 ADC, the $CD4^+$ T cells treated for five days with the different antibodies or ADCs (isotype control antibody, 140G5 mAb, 140G5-PNU mAb conjugate, 136B5 mAb, or 136B5-PNU mAb conjugate) were evaluated for the frequency of HIV infected cells using a quantitative viral outgrowth assay. In this assay, the antibody or ADC treated cells from an HIV infected patients are either left unstimulated or stimulated with anti-CD3/anti-CD28 antibodies then incubated at different dilutions in the presence of allogenic CD8-depleted PBMCs. Performing the tests with different dilutions of $CD4^+$ T cells from each sample allows for an estimate of the frequency of cells containing replication competent virus after the five-day treatment with antibodies or ADCs. Following a 14-day incubation of $CD4^+$ T cells and allogenic CD8-depleted PBMCs, samples are tested in both a p24 ELISA and for the presence of HIV RNA in order to establish the frequency of cells containing replication competent virus. In accordance with the specific depletion of PD-1 high cells shown in FIG. **20**, an increased percentage of PD-1 high cells that are Annexin V or Aqua positive was observed indicating increased levels of cell undergoing apoptosis and cell death, respectively (FIGS. **21***a* and **21***b*). In the viral outgrown assay shown in FIG. **22**, samples of $CD4^+$ T cells from an HIV infected donor that were treated with IgG1 isotope control antibody, anti-PD-1 antibodies (136B5 or 140G5) or left without treatment for five days all have a similar frequency of cells containing replication competent virus (16 to 28 HIV-1 RNA positive cells per million (RUPM)). However, in samples treated with anti-PD-1 ADCs (140G5-PNU mAb conjugate, 136B5 mAb, or 136B5-PNU mAb conjugate) there is a significant decrease in the frequency of infected cells that corresponds with a 4- to 5-fold reduction in cells that can produce infectious virus. These results have been reproduced in several separate experiments with up to a 10-fold reduction in RUPM associated with a five day anti-PD-1 ADC treatment. As such, these studies provide an in vitro proof of principle for the concept that an anti-PD-1 ADC could be an effective therapy for the depletion of infected cells from HIV-1 positive patients.

Example 7

Humanization of Mouse Anti-PD-1 Antibodies

The mouse IgG1 antibody sequences for select anti-PD-1 clones were compared against a human immunoglobulin germ line V gene database to find heavy and light chain frameworks most similar to those of mouse antibodies. Using these framework sequences, a combinatorial library was designed and used to construct a phage display library that incorporated the heavy and light chain CDR loops of the antibodies to be humanized. The phage library was then used in panning experiments against recombinant human PD-1 in an Fc fusion construct. A phage ELISA was used to evaluate the humanized anti-PD-1 output phage that bound recombinant PD-1. Fab-fragment DNA from positive clones were introduced into a FASEBA (fast screening for expression, biophysical-properties and affinity) library and used for the production of Fab protein fragments. These Fabs were evaluated for expression level, protein stability/biophysical properties and for affinity to recombinant human Fc-PD-1 proteins as determined by Biacore studies. The 137F2 and 135C12 mouse antibody clones of Table 2 were humanized in this manner and the resulting VH and VL sequences for clones with the desired expression, stability and affinity properties are shown below. Biacore affinity measurements of the 137F2 and 135C12 humanized Fab clones for human and monkey Fc-PD-1 proteins are shown in Tables 6 and 7, respectively. The amino acid sequences of these humanized antibodies are shown below.

A. Humanized 137F2 heavy chain sequences

1. Mouse VH reference sequence
QVQLQQPGAELVRPGTSVKMSCKAAGYTFTNYWIGWIKQRPGHGLEWIGDIYPGGGYTNY
NEKFKGKATLTADTSSSTAYMQVSSLTSEDTGIYYCARGYDFVLDRWGQGTSVTVSS (SEQ
ID NO. 169)

2. A35796-VH
QMQLVQSGPEVKKPGTSVKVSCKASGFTFTNYWIGWVRQAPGQALEWMGDIYPGGGYTN
YNEKFKGRVTITADKSTSTAYMELSSLRSEDTAVYYCARGYDFVLDRWGQGTTVTVSS
(SEQ ID NO. 170)

3. A35793-VH
QMQLVQSGPEVKKPGTSVKVSCKASGFTFTNYWIGWVRQAPGQALEWMGDIYPGGGYTN
YNEKFKGRVTITADKSTSTAYMELSSLRSEDTAVYYCARGYDFVLDRWGQGTTVTVSS
(SEQ ID NO. 171)

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4. A35818-VH
QMQLVQSGPEVKKPGTSVKVSCKASGFTFTNYWIGWVRQAPGQALEWMGDIYPGGGYTN
YNEKFKGRVTITADKSTSTAYMELSSLRSEDTAVYYCARGYDFVLDRWGQGTTVTVSS
(SEQ ID NO. 172)

5. A35795-VH
QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYWIGWVRQAPGQGLEWMGDIYPGGGYTN
YNEKFKGRVTITADKSTSTAYMELSSLRSEDTAVYYCARGYDFVLDRWGQGTTVTVSS
(SEQ ID NO. 173)

6. A35797-VH
EVQLVQSGAEVKKHGESLKISCKGSGYSFTNYWIGWVRQATGQGLEWMGDIYPGGGYTNY
NEKFKGRVTITADKSTSTAYMELSSLRSEDTAVYYCARGYDFVLDRWGQGTTVTVSS (SEQ
ID NO. 174)

7. A35799-VH
QMQLVQSGAEVKKTGSSVKVSCKASGYTFTNYWIGWVRQMPGKGLEWMGDIYPGGGYTN
YNEKFKGRVTITADKSTSTAYMELSSLRSEDTAVYYCARGYDFVLDRWGQGTTVTVSS
(SEQ ID NO. 175)

8. A35805-VH
QVQLVQSGSELKKPGASVKVSCKASGYTFTNYWIGWVRQAPGKGLEWMGDIYPGGGYTN
YNEKFKGRVTITADKSTSTAYMELSSLRSEDTAVYYCARGYDFVLDRWGQGTTVTVSS
(SEQ ID NO. 176)

B. Humanized 137F2 light chain sequences

1. Mouse VL reference sequence
DIVMSQSPSSLAVSTGEKVTMTCKSSQSLFNSETQKNYLAWYQQKPGQPPKLLIFWASTRE
SGVPDRFLGSGSGTDFTLTISSVQAEDLAVYYCKQSYTLRTFGGGTKLEIK (SEQ ID NO.
177).

2. A35796-VL
DVVMTQSPAFLSVTPGEKVTITCKSSQSLFNSETQKNYLAWYQQKPGQPPKWYWASTRE
SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCKQSYTLRTFGGGTKLEIK (SEQ ID NO.
178)

3. A35793-VL
DVVMTQSPAFLSVTPGEKVTITCKSSQSLFNSETQKNYLAWYQQKPGQPPKLLIYWASTRE
SGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCKQSYTLRTFGGGTKLEIK (SEQ ID NO.
179)

4. A35818-VL
DVVMTQSPAFLSVTPGEKVTITCKSSQSLFNSETQKNYLAWYQQKPGQAPRLLIYWASTRE
SGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCKQSYTLRTFGGGTKLEIK (SEQ ID NO.
180)

5. A35795-VL
DVVMTQSPAFLSVTPGEKVTITCKSSQSLFNSETQKNYLAWYQQKPGQAPRLLIYWASTRE
SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCKQSYTLRTFGGGTKLEIK (SEQ ID NO.
181)

6. A35797-VL
DIQMTQSPSSLSASVGDRVTITCKSSQSLFNSETQKNYLAWYQQKPGQPPKWYWASTRE
SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCKQSYTLRTFGGGTKLEIK (SEQ ID NO.
182)

7. A35799-VL
DVVMTQSPAFLSVTPGEKVTITCKSSQSLFNSETQKNYLAWYQQKPGQPPKWYWASTRE
SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCKQSYTLRTFGGGTKLEIK (SEQ ID NO.
183)

8. A35805-VL
DVVMTQSPAFLSVTPGEKVTITCKSSQSLFNSETQKNYLAWYQQKPGQPPKWYWASTRE
SGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCKQSYTLRTFGGGTKLEIK (SEQ ID NO.
184)

C. Humanized 135C12 heavy chain sequences

1. Mouse VH reference sequence
EVQLHQSGPELLKPGASVRMSCKASGYTFTNFYIHWVKQSHGKSIEWIGSIYPNYGDTAYN
QKFKDKATLTVDKSSSTAYMALRSLTSEDSAVYYCARGYSYAMDYWGQGTSVTVSS (SEQ
ID NO. 185)

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2. A35775-VH
VHEVQLVQSGAEVKKPGESLKISCKGSGYSFTNFYIHWVRQAPGQRLEWMGSIYPNYGDT
AYNQKFKDRFVFSLDTSVSTAYLQISSLKAEDTAVYYCARGYSYAMDYWGQGTTVTVSS
(SEQ ID NO. 186)

3. A35783-VH
EVQLVQSGAEVKKPGESLKISCKGSGYSFTNFYIHWVRQARGQRLEWIGSIYPNYGDTAYN
QKFKDRFVFSLDTSVSTAYLQISSLKAEDTAVYYCARGYSYAMDYWGQGTTVTVSS (SEQ
ID NO. 187)

4. A35774-VH
EVQLVQSGAEVKKPGESLKISCKGSGYSFTNFYIHWVRQAPGQRLEWMGSIYPNYGDTAY
NQKFKDRFVFSLDTSVSTAYLQISSLKAEDTAVYYCARGYSYAMDYWGQGTTVTVSS (SEQ
ID NO. 188)

5. A36443-VH
EVQLVQSGAEVKKPGATVKISCKVSGYTFTNFYIHWVRQARGQRLEWIGSIYPNYGDTAYN
QKFKDRVTITADKSTSTAYMELSSLRSEDTAVYYCARGYSYAMDYWGQGTTVTVSS (SEQ
ID NO. 189)

6. A35777-VH
EVQLVQSGAEVKKPGATVKISCKVSGYTFTNFYIHWVRQAPGKGLEWMGSIYPNYGDTAYN
QKFKDRVTITADKSTSTAYMELSSLRSEDTAVYYCARGYSYAMDYWGQGTTVTVSS (SEQ
ID NO. 190)

7. A35789-VH
EVQLVQSGAEVKKPGESLKISCKGSGYSFTNFYIHWVRQMPGKGLEWMGSIYPNYGDTAY
NQKFKDRVTITADKSTSTAYMELSSLRSEDTAVYYCARGYSYAMDYWGQGTTVTVSS (SEQ
ID NO. 191)

8. A36448-VH
EVQLVQSGAEVKKPGESLKISCKGSGYSFTNFYIHWVRQMPGKGLEWMGSIYPNYGDTAY
NQKFKDRFVFSLDTSVSTAYLQISSLKAEDTAVYYCARGYSYAMDYWGQGTTVTVSS (SEQ
ID NO. 192)

9. A36437-VH
EVQLVQSGAEVKKPGESLKISCKGSGYSFTNFYIHWVRQMPGKGLEWMGSIYPNYGDTAY
NQKFKDRFVFSLDTSVSTAYLQISSLKAEDTAVYYCARGYSYAMDYWGQGTTVTVSS (SEQ
ID NO. 193)

D. Humanized 135C12 Light chain sequences

1. Mouse VL reference sequence
NIVMTQSPKSMSMSVGERVTLTCKASENVVTYVSWYQQKPEQSPKLLIYGASNRYTGVPDR
FTGSGSATDFTLTISSVQAEDLADYHCGQGYSYPYTFGGGTKLEIK (SEQ ID NO. 194)

2. A35775-VL
DIQMTQSPSSVSASVGDRVTITCSASQGISGDLNWYQQKPGQAPRLLIYHTSSLHSGVPSRF
SGSGSGTDFTLTISSLQPEDFATYYCQYYSKDLLTFGGGTKLEIK (SEQ ID NO. 195)

3. A35783-VL
DIQMTQSPSSLSASVGDRVTITCSASQGISGDLNWYQQKPGKTPKLLIYHTSSLHSGVPSRF
SGSGSGTDFTLTISSLQPEDFATYYCQYYSKDLLTFGGGTKLEIK (SEQ ID NO. 196)

4. 35774-VL
DIQMTQSPSSVSASVGDRVTITCSASQGISGDLNWYQQKPGKAPKLLIYHTSSLHSGVPSRF
SGSGSGTDFTLTISSLQPEDFATYYCQYYSKDLLTFGGGTKLEIK (SEQ ID NO. 197)

5. A36443-VL
DIQMTQSPSSVSASVGDRVTITCSASQGISGDLNWYQQKPGQAPRLLIYHTSSLHSGVPSRF
SGSGSGTEFTLTISRLEPEDFAVYYCQYYSKDLLTFGGGTKLEIK (SEQ ID NO. 198)

6. A35777-VL
DIQMTQSPSTLSASVGDRVTITCSASQGISGDLNWYQQKPGQAPRLLIYHTSSLHSGVPSRF
SGSGSGTDFTLTISSLQPEDFATYYCQYYSKDLLTFGGGTKLEIK (SEQ ID NO. 199)

7. A35789-VL
DIQMTQSPSSVSASVGDRVTITCSASQGISGDLNWYQQKPGQAPRLLIYHTSSLHSGIPARF
SGSGSGTDFTLTISRLEPEDFAVYYCQYYSKDLLTFGGGTKLEIK (SEQ ID NO. 200)

8. A36448-VL
DIQMTQSPSTLSASVGDRVTITCSASQGISGDLNWYQQKPGKTPKLLIYHTSSLHSGVPSRF
SGSGSGTDFTLTISSLQPEDFATYYCQYYSKDLLTFGGGTKLEIK (SEQ ID NO. 201)

9. A36437-VL
DIQMTQSPSTLSASVGDRVTITCSASQGISGDLNWYQQKPGQAPRLLIYHTSSLHSGIPARF
SGSGSGTDFTLTISSLQPEDFAVYYCQYYSKDLLTFGGGTKLEIK (SEQ ID NO. 202)

Biacore binding affinity measurements for each of these humanized antibodies are presented in Tables 6 and 7 below.

TABLE 6

Biacore binding affinity measurements of humanized anti-PD-1 Fab clones relating to 137F2 for human and monkey PD-1

	Human PD-1			Monkey PD-1		
Ligand	ka (M^{-1}/s^{-1})	kd (s^{-1})	KD (M)	ka (M^{-1}/s^{-1})	kd (s^{-1})	KD (M)
mouse 137F2A11	1.37E+05	2.10E−04	1.54E−09	1.38E+05	3.05E−04	2.22E−09
A35796	1.04E+05	1.23E−04	1.18E−09	9.53E+04	9.81E−05	1.03E−09
A35793	1.04E+05	9.49E−05	9.12E−10	9.32E+04	1.05E−04	1.13E−09
A35818	9.88E+04	1.04E−04	1.06E−09	9.14E+04	1.16E−04	1.27E−09
A35795	1.03E+05	8.24E−05	7.97E−10	9.25E+04	1.52E−04	1.64E−09
A35797	1.00E+05	8.02E−05	8.02E−10	9.37E+04	1.06E−04	1.13E−09
A35799	1.01E+05	7.43E−05	7.34E−10	8.97E+04	1.69E−04	1.88E−09
A35805	9.37E+04	8.78E−05	9.37E−10	8.82E+04	9.49E−05	1.08E−09

TABLE 7

Biacore binding affinity measurements of humanized anti-PD-1 Fab clones relating to 135C12 for human and monkey PD-1

	Human PD-1			Monkey PD-1		
Ligand	ka (M^{-1}/s^{-1})	kd (s^{-1})	KD (M)	ka (M^{-1}/s^{-1})	kd (s^{-1})	KD (M)
mouse 135C12	9.52E+04	1.52E−04	1.60E−09	8.40E+04	2.38E−04	2.83E−09
A35775	8.02E+04	2.03E−04	2.54E−09	6.05E+04	3.47E−04	5.73E−09
A35783	7.68E+04	1.96E−04	2.55E−09	4.21E+05	8.00E−04	1.90E−09
A35774	8.09E+04	2.11E−04	2.61E−09	6.93E+04	1.94E−04	2.79E−09
A36443	7.12E+04	2.15E−04	3.02E−09	9.49E+04	5.85E−04	6.16E−09
A35777	6.86E+04	3.52E−04	5.13E−09	1.15E+05	5.75E−04	5.00E−09
A35789	7.01E+04	2.93E−04	4.17E−09	6.67E+04	4.13E−04	6.19E−09
A36448	8.96E+04	3.86E−04	4.31E−09	NA	NA	NA
A36437	7.10E+04	3.17E−04	4.46E−09	6.07E+04	3.68E−04	6.07E−09

While certain embodiments have been described in terms of the preferred embodiments, it is understood that variations and modifications will occur to those skilled in the art. Therefore, it is intended that the appended claims cover all such equivalent variations that come within the scope of the following claims.

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<400> SEQUENCE: 33

Tyr Ile Asn Tyr Ser Gly Tyr Thr Asn Tyr Asn Pro Phe Leu Lys Ser
1 5 10 15

<210> SEQ ID NO 34
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

Asn Ile Tyr Pro Gly Ser Ser Ser Thr Asp Tyr Asn Glu Lys Phe Lys
1 5 10 15

Ser

<210> SEQ ID NO 35
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

Trp Ile Phe Pro Gly Asp Gly Lys Thr Asn Tyr Asn Glu Lys Phe Arg
1 5 10 15

Asp

<210> SEQ ID NO 36
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

Ser Ile Asn Thr Gly Gly Tyr Ser Thr Tyr Tyr Pro Asp Asn Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 37
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

Asp Ile Tyr Pro Gly Ser Glu Tyr Glu Asn Tyr Asn Glu Lys Phe Lys
1 5 10 15

Gly

<210> SEQ ID NO 38
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 38

Arg Ile Asp Pro Ala His Gly Asn Val Ile Tyr Ala Ser Lys Phe Arg
1 5 10 15

Asp

<210> SEQ ID NO 39
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 39

Arg Ile Asp Leu Ala Asn Asp Asp Ile Leu Tyr Ala Ser Lys Phe Gln
1 5 10 15

Gly

<210> SEQ ID NO 40
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 40

Ser Ile Tyr Pro Asn Tyr Gly Asp Thr Ala Tyr Asn Gln Lys Phe Lys
1 5 10 15

Asp

<210> SEQ ID NO 41
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 41

Arg Ile Asp Pro Ala Arg Asp Asn Ile Ile Tyr Ala Ser Lys Phe Arg
1 5 10 15

Asp

<210> SEQ ID NO 42
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 42

Arg Ile Asp Pro Ala Asn Gly Glu Ser Arg Tyr Ala Pro Gln Phe Gln
1 5 10 15

Asp

<210> SEQ ID NO 43
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 43

Gly Ile Ser Thr Gly Gly Ala Asp Thr Tyr Tyr Ala Asp Ser Met Lys
1 5 10 15

Gly

<210> SEQ ID NO 44
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 44

Ser Ile Ser Gly Gly Gly Asp Asn Thr Tyr Tyr Pro Asp Asn Leu Lys
1 5 10 15

Gly

<210> SEQ ID NO 45
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 45

Asp Ile Tyr Pro Gly Gly Asp His Lys Asn Tyr Asn Glu Lys Phe Lys
1 5 10 15

Asp

<210> SEQ ID NO 46
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 46

Thr Ile Thr Gly Gly Gly Val Asn Thr Tyr Tyr Pro Asp Thr Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 47
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 47

Thr Asp Tyr Arg Gly Tyr Tyr Tyr Ala Met Asp Tyr
1 5 10

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<210> SEQ ID NO 48
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 48

Gly Tyr Ser Tyr Ala Met Asp Tyr
1 5

<210> SEQ ID NO 49
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 49

Gly Tyr Ser Tyr Ala Met Asp Tyr
1 5

<210> SEQ ID NO 50
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 50

Gly Arg Ser Tyr Asp Gly Ser Phe Asp Tyr
1 5 10

<210> SEQ ID NO 51
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 51

Asp Leu Asp Asp Phe Tyr Val Gly Ser His Glu Asp Phe Asp Tyr
1 5 10 15

<210> SEQ ID NO 52
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 52

Gly Arg Ser Tyr Asp Gly Ser Phe Asp Tyr
1 5 10

<210> SEQ ID NO 53
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 53

Glu Glu Tyr Asp Tyr Asp Asn Tyr
1 5

<210> SEQ ID NO 54
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 54

Gly Tyr Asp Phe Val Leu Asp Arg
1 5

<210> SEQ ID NO 55
<211> LENGTH: 9

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 55

Gln Arg Gly Glu Asn Leu Phe Ala His
1 5

<210> SEQ ID NO 56
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 56

Tyr Gly Gly Ser Tyr Pro Trp Asn Phe Asp Val
1 5 10

<210> SEQ ID NO 57
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 57

Gly Leu Tyr Trp Tyr Phe Asp Val
1 5

<210> SEQ ID NO 58
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 58

Asn Asp Phe Asp Arg Gly Val Tyr
1 5

<210> SEQ ID NO 59
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 59

Asp Asp Tyr Asn Trp Phe Ala Tyr
1 5

<210> SEQ ID NO 60
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 60

Gly Tyr Asp Phe Val Leu Asp His
1 5

<210> SEQ ID NO 61
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 61

Ile Tyr Tyr Asp Tyr Gly Glu Gly Asp Phe
1 5 10

<210> SEQ ID NO 62
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 62

Ile Tyr Tyr Asp Tyr Gly Glu Gly Asp Tyr
1 5 10

<210> SEQ ID NO 63
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 63

Gly Tyr Ser Tyr Ala Met Asp Tyr
1 5

<210> SEQ ID NO 64
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 64

Ile Tyr Tyr Asp Tyr Gly Glu Gly Asp Tyr
1 5 10

<210> SEQ ID NO 65
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 65

Thr Asp Tyr Arg Gly Tyr Tyr Tyr Ala Met Asp Tyr
1 5 10

<210> SEQ ID NO 66
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 66

Leu Ser His Tyr Tyr Asp Gly Ile Pro Leu Asp Cys
1 5 10

<210> SEQ ID NO 67
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 67

Val Arg Gln Leu Gly Leu His Arg Ala Ala Met Asp Tyr
1 5 10

<210> SEQ ID NO 68
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 68

Gly Phe Asp Phe Val Leu Asp Tyr
1 5

<210> SEQ ID NO 69
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 69

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Gln Ala Ile Tyr Asp Gly His Tyr Val Leu Asp Tyr
1 5 10

<210> SEQ ID NO 70
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 70

Lys Ser Ser Gln Ser Val Leu Tyr Ser Ser Asn Gln Lys Asn Tyr Leu
1 5 10 15

Ala

<210> SEQ ID NO 71
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 71

Ser Ala Ser Gln Gly Ile Ser Asp Gly Leu Asn
1 5 10

<210> SEQ ID NO 72
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 72

Ser Ala Ser Gln Gly Ile Ser Asn Gly Leu Asn
1 5 10

<210> SEQ ID NO 73
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 73

Lys Ala Ser Gln Asp Ile Asn Lys Tyr Ile Ala
1 5 10

<210> SEQ ID NO 74
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 74

Arg Ser Ser Gln Ser Ile Val Tyr Ser Asn Gly Asn Thr Tyr Leu Glu
1 5 10 15

<210> SEQ ID NO 75
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 75

Lys Ala Ser Gln Asp Ile Asn Lys Tyr Met Ala
1 5 10

<210> SEQ ID NO 76
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 76

Lys Ala Ser Gln Asn Val Gly Thr Asn Val Gly
1 5 10

<210> SEQ ID NO 77
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 77

Lys Ser Ser Gln Ser Leu Phe Asn Ser Glu Thr Gln Lys Asn Tyr Leu
1 5 10 15

Ala

<210> SEQ ID NO 78
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 78

Leu Ala Ser Gln Thr Ile Gly Thr Trp Leu Ala
1 5 10

<210> SEQ ID NO 79
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 79

Arg Ser Ser Gln Thr Ile Val His Asn Asn Gly Asp Thr Tyr Leu Glu
1 5 10 15

<210> SEQ ID NO 80
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 80

Lys Ser Ser Gln Ser Leu Phe Asn Ser Gly Thr Arg Lys Asn Tyr Leu
1 5 10 15

Ala

<210> SEQ ID NO 81
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 81

Lys Ala Ser Gln Asn Val Asp Thr Asn Val Ala
1 5 10

<210> SEQ ID NO 82
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 82

Lys Ser Ser Gln Ser Leu Leu Asn Ser Gly Asn Gln Lys Asn Tyr Leu
1 5 10 15

Thr

<210> SEQ ID NO 83
<211> LENGTH: 17

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 83

Lys Ser Ser Gln Ser Leu Phe Asn Ser Gly Thr Arg Lys Ser Tyr Leu
1 5 10 15

Ala

<210> SEQ ID NO 84
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 84

His Ala Ser Gln Asn Ile Asn Val Trp Leu Ser
1 5 10

<210> SEQ ID NO 85
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 85

His Ala Ser Gln Asn Ile Asn Val Trp Leu Ser
1 5 10

<210> SEQ ID NO 86
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 86

Ser Ala Ser Gln Gly Ile Ser Gly Asp Leu Asn
1 5 10

<210> SEQ ID NO 87
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 87

His Ala Ser Gln Asn Ile Asn Val Trp Leu Ser
1 5 10

<210> SEQ ID NO 88
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 88

Lys Ser Ser Gln Ser Val Leu Tyr Ser Ser Asn Gln Lys Asn Tyr Leu
1 5 10 15

Ala

<210> SEQ ID NO 89
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 89

Arg Ala Ser Glu Ser Val Asp Asn Ser Gly Val Ser Phe Leu Thr
1 5 10 15

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<210> SEQ ID NO 90
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 90

Lys Ala Ser Gln Ser Val Ser Asp Asp Val Ser
1 5 10

<210> SEQ ID NO 91
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 91

Lys Ser Ser Gln Ser Leu Phe Asn Ser Gly Thr Arg Lys Asn Tyr Leu
1 5 10 15

Ala

<210> SEQ ID NO 92
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 92

Arg Thr Ser Gly Asn Ile His Asn Tyr Leu Ala
1 5 10

<210> SEQ ID NO 93
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 93

Trp Ala Ser Thr Arg Glu Ser
1 5

<210> SEQ ID NO 94
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 94

His Thr Ser Thr Leu His Ser
1 5

<210> SEQ ID NO 95
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 95

His Thr Ser Thr Leu His Ser
1 5

<210> SEQ ID NO 96
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 96

Tyr Thr Ser Thr Leu Arg Pro
1 5

<210> SEQ ID NO 97
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 97

Lys Val Ser His Arg Phe Ser
1 5

<210> SEQ ID NO 98
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 98

Tyr Thr Ser Thr Leu Arg Pro
1 5

<210> SEQ ID NO 99
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 99

Ser Ala Ser Tyr Arg Tyr Asn
1 5

<210> SEQ ID NO 100
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 100

Trp Ala Ser Thr Arg Glu Ser
1 5

<210> SEQ ID NO 101
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 101

Ala Ala Thr Ser Leu Ala Asp
1 5

<210> SEQ ID NO 102
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 102

Lys Ile Ser Asn Arg Phe Phe
1 5

<210> SEQ ID NO 103
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 103

Trp Ala Ser Thr Arg Asp Ser
1 5

<210> SEQ ID NO 104
<211> LENGTH: 7

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 104

Ser Ala Ser Tyr Arg Tyr Asn
1 5

<210> SEQ ID NO 105
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 105

Trp Ala Ser Thr Arg Glu Ser
1 5

<210> SEQ ID NO 106
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 106

Trp Ala Ser Thr Arg Glu Thr
1 5

<210> SEQ ID NO 107
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 107

Lys Ala Ser Asn Leu His Thr
1 5

<210> SEQ ID NO 108
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 108

Lys Ala Ser Asn Leu His Thr
1 5

<210> SEQ ID NO 109
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 109

His Thr Ser Ser Leu His Ser
1 5

<210> SEQ ID NO 110
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 110

Lys Ala Ser Asn Leu His Thr
1 5

<210> SEQ ID NO 111
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 111

Trp Ala Ser Thr Arg Glu Ser
1 5

<210> SEQ ID NO 112
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 112

Ala Ala Ser Asn Gln Gly Ser
1 5

<210> SEQ ID NO 113
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 113

Ser Ala Phe Phe Arg Tyr Pro
1 5

<210> SEQ ID NO 114
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 114

Trp Ala Ser Thr Arg Glu Ser
1 5

<210> SEQ ID NO 115
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 115

Asn Val Lys Thr Leu Thr Asp
1 5

<210> SEQ ID NO 116
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 116

His Gln Tyr Leu Ser Ser Tyr Thr
1 5

<210> SEQ ID NO 117
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 117

Gln Gln Tyr Ser Lys Phe Pro Leu Thr
1 5

<210> SEQ ID NO 118
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 118

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Gln Gln Tyr Ser Lys Phe Pro Leu Thr
1 5

<210> SEQ ID NO 119
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 119

Leu Gln Tyr Asp Asn Leu Trp Thr
1 5

<210> SEQ ID NO 120
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 120

Phe Gln Gly Ser His Val Pro Tyr Thr
1 5

<210> SEQ ID NO 121
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 121

Leu Gln Tyr Asp Asn Leu Trp Thr
1 5

<210> SEQ ID NO 122
<211> LENGTH: 9
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 122

Gln Gln Tyr Asn Thr Tyr Pro Trp Thr
1 5

<210> SEQ ID NO 123
<211> LENGTH: 8
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<400> SEQUENCE: 123

Lys Gln Ser Tyr Thr Leu Arg Thr
1 5

<210> SEQ ID NO 124
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 124

Gln Gln Leu Tyr Ser Thr Pro Trp Thr
1 5

<210> SEQ ID NO 125
<211> LENGTH: 9
<212> TYPE: PRT
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<400> SEQUENCE: 125

Phe Gln Gly Ser His Val Pro Tyr Thr

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1 5

<210> SEQ ID NO 126
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 126

Lys Gln Ser Tyr Asn Leu Tyr Thr
1 5

<210> SEQ ID NO 127
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 127

Gln Gln Tyr Asn Asn Tyr Pro Tyr Thr
1 5

<210> SEQ ID NO 128
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 128

Gln Ser Asp Tyr Ser Tyr Pro Leu Thr
1 5

<210> SEQ ID NO 129
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 129

Met Gln Ser Tyr Asn Leu Arg Thr
1 5

<210> SEQ ID NO 130
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 130

Gln Gln Gly Gln Ser Trp Pro Leu Thr
1 5

<210> SEQ ID NO 131
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 131

Gln Gln Gly Gln Ser Tyr Pro Leu Thr
1 5

<210> SEQ ID NO 132
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 132

Gln Tyr Tyr Ser Lys Asp Leu Leu Thr
1 5

<210> SEQ ID NO 133
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 133

Gln Gln Gly Gln Ser Trp Pro Leu Thr
1 5

<210> SEQ ID NO 134
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 134

His Gln Tyr Leu Ser Ser Tyr Thr
1 5

<210> SEQ ID NO 135
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 135

Gln Gln Thr Lys Glu Val Pro Trp Thr
1 5

<210> SEQ ID NO 136
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 136

Gln Gln Asp Tyr Ser Ser Pro Leu Thr
1 5

<210> SEQ ID NO 137
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 137

Met Gln Ser Phe Asn Leu Arg Thr
1 5

<210> SEQ ID NO 138
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 138

Gln Gln Phe Trp Ser Ile Pro Trp Thr
1 5

<210> SEQ ID NO 139
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 139

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1 5 10 15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Ala Ser Pro Ala Arg Pro Trp
20 25 30

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Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
        35                  40                  45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
    50                  55                  60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65                  70                  75                  80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
                85                  90                  95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
            100                 105                 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
        115                 120                 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
        275                 280                 285


<210> SEQ ID NO 140
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 140

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1               5                   10                  15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Ala Pro Ala
            20                  25                  30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
        35                  40                  45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
    50                  55                  60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65                  70                  75                  80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
                85                  90                  95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
            100                 105                 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
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        115                 120                 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
        275                 280                 285


<210> SEQ ID NO 141
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 141

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1               5                   10                  15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
            20                  25                  30

Asn Pro Pro Lys Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
        35                  40                  45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
    50                  55                  60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65                  70                  75                  80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
                85                  90                  95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
            100                 105                 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
        115                 120                 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205
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Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
        275                 280                 285


<210> SEQ ID NO 142
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 142

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1               5                   10                  15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
            20                  25                  30

Asn Pro Pro Thr Phe Ala Ala Ala Ala Leu Val Val Thr Glu Gly Asp
        35                  40                  45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
    50                  55                  60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65                  70                  75                  80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
                85                  90                  95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
            100                 105                 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
        115                 120                 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
        275                 280                 285


<210> SEQ ID NO 143
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<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 143

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1 5 10 15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
20 25 30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Ala
35 40 45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
50 55 60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65 70 75 80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
85 90 95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
100 105 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
115 120 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
130 135 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145 150 155 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
165 170 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
180 185 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
195 200 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
210 215 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225 230 235 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
245 250 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
260 265 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
275 280 285

<210> SEQ ID NO 144
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 144

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1 5 10 15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
20 25 30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
35 40 45

Ala Ala Ala Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
50 55 60

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Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65                  70                  75                  80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
                85                  90                  95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
            100                 105                 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
        115                 120                 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
        275                 280                 285


<210> SEQ ID NO 145
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 145

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1               5                   10                  15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
            20                  25                  30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
        35                  40                  45

Asn Ala Thr Ala Ala Cys Ala Phe Ser Asn Thr Ser Glu Ser Phe Val
    50                  55                  60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65                  70                  75                  80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
                85                  90                  95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
            100                 105                 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
        115                 120                 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
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145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
        275                 280                 285


<210> SEQ ID NO 146
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 146

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1               5                   10                  15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
            20                  25                  30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
        35                  40                  45

Asn Ala Thr Phe Thr Cys Ser Phe Ala Ala Thr Ser Glu Ser Phe Val
    50                  55                  60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65                  70                  75                  80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
                85                  90                  95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
            100                 105                 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
        115                 120                 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240
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Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
        275                 280                 285


<210> SEQ ID NO 147
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 147

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1               5                   10                  15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
            20                  25                  30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
        35                  40                  45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Ala Ala Phe Val
    50                  55                  60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65                  70                  75                  80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
                85                  90                  95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
            100                 105                 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
        115                 120                 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
        275                 280                 285


<210> SEQ ID NO 148
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 148
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Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1               5                  10                  15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
            20                  25                  30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
        35                  40                  45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Ala
    50                  55                  60

Leu Ala Trp Ala Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65                  70                  75                  80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
                85                  90                  95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
            100                 105                 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
        115                 120                 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
        275                 280                 285


<210> SEQ ID NO 149
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 149

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1               5                  10                  15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
            20                  25                  30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
        35                  40                  45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
    50                  55                  60

Leu Asn Trp Tyr Arg Met Ser Pro Ala Asn Ala Ala Asp Lys Leu Ala
65                  70                  75                  80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
                85                  90                  95
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Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
            100                 105                 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
        115                 120                 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
        275                 280                 285


<210> SEQ ID NO 150
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 150

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1               5                   10                  15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
            20                  25                  30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
        35                  40                  45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
    50                  55                  60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Ala Asp Ala Leu Ala
65                  70                  75                  80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
                85                  90                  95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
            100                 105                 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
        115                 120                 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
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            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
        275                 280                 285


<210> SEQ ID NO 151
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 151

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1               5                   10                  15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
            20                  25                  30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
        35                  40                  45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
    50                  55                  60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65                  70                  75                  80

Ala Phe Pro Glu Ala Ala Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
                85                  90                  95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
            100                 105                 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
        115                 120                 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270
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```
Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
        275                 280                 285


<210> SEQ ID NO 152
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 152

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1               5                   10                  15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
            20                  25                  30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
        35                  40                  45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
    50                  55                  60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65                  70                  75                  80

Ala Phe Pro Glu Asp Arg Ser Gln Ala Ala Gly Asp Cys Arg Phe Arg
                85                  90                  95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
            100                 105                 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
        115                 120                 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
        275                 280                 285


<210> SEQ ID NO 153
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 153

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1               5                   10                  15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
            20                  25                  30
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Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
        35                  40                  45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
    50                  55                  60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65                  70                  75                  80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Ala Ala Cys Arg Phe Arg
                85                  90                  95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
            100                 105                 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
        115                 120                 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
        275                 280                 285


<210> SEQ ID NO 154
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 154

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1               5                   10                  15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
            20                  25                  30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
        35                  40                  45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
    50                  55                  60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65                  70                  75                  80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Ala
                85                  90                  95

Val Ala Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
            100                 105                 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
        115                 120                 125
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Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
        275                 280                 285


<210> SEQ ID NO 155
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 155

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1               5                   10                  15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
            20                  25                  30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
        35                  40                  45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
    50                  55                  60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65                  70                  75                  80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
                85                  90                  95

Val Thr Gln Leu Pro Ala Gly Ala Asp Phe His Met Ser Val Val Arg
            100                 105                 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
        115                 120                 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
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    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
        275                 280                 285


<210> SEQ ID NO 156
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 156

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1               5                   10                  15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
            20                  25                  30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
        35                  40                  45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
    50                  55                  60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65                  70                  75                  80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
                85                  90                  95

Val Thr Gln Leu Pro Asn Gly Arg Ala Phe His Met Ser Val Val Arg
            100                 105                 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
        115                 120                 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
        275                 280                 285


<210> SEQ ID NO 157
<211> LENGTH: 288
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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 157

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1 5 10 15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
20 25 30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
35 40 45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
50 55 60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65 70 75 80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
85 90 95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe Ala Met Ala Val Val Arg
100 105 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
115 120 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
130 135 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145 150 155 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
165 170 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
180 185 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
195 200 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
210 215 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225 230 235 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
245 250 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
260 265 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
275 280 285

<210> SEQ ID NO 158
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 158

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1 5 10 15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
20 25 30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
35 40 45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
50 55 60

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Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65                  70                  75                  80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
                85                  90                  95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Ala Ala
            100                 105                 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
        115                 120                 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
        275                 280                 285


<210> SEQ ID NO 159
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 159

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1               5                   10                  15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
            20                  25                  30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
        35                  40                  45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
    50                  55                  60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65                  70                  75                  80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
                85                  90                  95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
            100                 105                 110

Ala Ala Ala Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
        115                 120                 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160
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Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
        275                 280                 285


<210> SEQ ID NO 160
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 160

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1               5                   10                  15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
            20                  25                  30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
        35                  40                  45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
    50                  55                  60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65                  70                  75                  80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
                85                  90                  95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
            100                 105                 110

Ala Arg Arg Asn Ala Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
        115                 120                 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
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                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
        275                 280                 285


<210> SEQ ID NO 161
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 161

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1               5                   10                  15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
            20                  25                  30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
        35                  40                  45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
    50                  55                  60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65                  70                  75                  80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
                85                  90                  95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
            100                 105                 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Ala Gly Ala Ser Ala
        115                 120                 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
        275                 280                 285


<210> SEQ ID NO 162
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 162

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
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1               5                   10                  15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
            20                  25                  30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
        35                  40                  45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
    50                  55                  60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65                  70                  75                  80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
                85                  90                  95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
            100                 105                 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
        115                 120                 125

Ala Pro Thr Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
        275                 280                 285


<210> SEQ ID NO 163
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 163

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1               5                   10                  15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
            20                  25                  30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
        35                  40                  45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
    50                  55                  60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65                  70                  75                  80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
                85                  90                  95
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Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
            100                 105                 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
        115                 120                 125

Ala Pro Lys Ala Gln Ile Thr Ala Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
        275                 280                 285


<210> SEQ ID NO 164
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 164

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1               5                   10                  15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
            20                  25                  30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
        35                  40                  45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
    50                  55                  60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65                  70                  75                  80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
                85                  90                  95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
            100                 105                 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
        115                 120                 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Ala Ala Ala Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190
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```
Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
        275                 280                 285


<210> SEQ ID NO 165
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 165

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1               5                   10                  15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
            20                  25                  30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
        35                  40                  45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
    50                  55                  60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65                  70                  75                  80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
                85                  90                  95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
            100                 105                 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
        115                 120                 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Ala Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
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275 280 285

<210> SEQ ID NO 166
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 166

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1 5 10 15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
20 25 30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
35 40 45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
50 55 60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65 70 75 80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
85 90 95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
100 105 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
115 120 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
130 135 140

Thr Glu Ala Ala Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145 150 155 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
165 170 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
180 185 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
195 200 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
210 215 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225 230 235 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
245 250 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
260 265 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
275 280 285

<210> SEQ ID NO 167
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 167

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1 5 10 15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
20 25 30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp

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        35                  40                  45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
    50                  55                  60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65                  70                  75                  80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
                85                  90                  95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
            100                 105                 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
        115                 120                 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala Ala Ala Ala Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
        275                 280                 285


<210> SEQ ID NO 168
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 168

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1               5                   10                  15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
            20                  25                  30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
        35                  40                  45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
    50                  55                  60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65                  70                  75                  80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
                85                  90                  95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
            100                 105                 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
        115                 120                 125
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Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Ala Ala Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
        275                 280                 285


<210> SEQ ID NO 169
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 169

Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Arg Pro Gly Thr
1               5                   10                  15

Ser Val Lys Met Ser Cys Lys Ala Ala Gly Tyr Thr Phe Thr Asn Tyr
            20                  25                  30

Trp Ile Gly Trp Ile Lys Gln Arg Pro Gly His Gly Leu Glu Trp Ile
        35                  40                  45

Gly Asp Ile Tyr Pro Gly Gly Gly Tyr Thr Asn Tyr Asn Glu Lys Phe
    50                  55                  60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Thr Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80

Met Gln Val Ser Ser Leu Thr Ser Glu Asp Thr Gly Ile Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Tyr Asp Phe Val Leu Asp Arg Trp Gly Gln Gly Thr Ser
            100                 105                 110

Val Thr Val Ser Ser
        115


<210> SEQ ID NO 170
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 170

Gln Met Gln Leu Val Gln Ser Gly Pro Glu Val Lys Lys Pro Gly Thr
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe Thr Asn Tyr
            20                  25                  30

Trp Ile Gly Trp Val Arg Gln Ala Pro Gly Gln Ala Leu Glu Trp Met
        35                  40                  45
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Gly Asp Ile Tyr Pro Gly Gly Gly Tyr Thr Asn Tyr Asn Glu Lys Phe
    50                  55                  60

Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Tyr Asp Phe Val Leu Asp Arg Trp Gly Gln Gly Thr Thr
            100                 105                 110

Val Thr Val Ser Ser
        115


<210> SEQ ID NO 171
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 171

Gln Met Gln Leu Val Gln Ser Gly Pro Glu Val Lys Lys Pro Gly Thr
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe Thr Asn Tyr
            20                  25                  30

Trp Ile Gly Trp Val Arg Gln Ala Pro Gly Gln Ala Leu Glu Trp Met
        35                  40                  45

Gly Asp Ile Tyr Pro Gly Gly Gly Tyr Thr Asn Tyr Asn Glu Lys Phe
    50                  55                  60

Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Tyr Asp Phe Val Leu Asp Arg Trp Gly Gln Gly Thr Thr
            100                 105                 110

Val Thr Val Ser Ser
        115


<210> SEQ ID NO 172
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 172

Gln Met Gln Leu Val Gln Ser Gly Pro Glu Val Lys Lys Pro Gly Thr
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe Thr Asn Tyr
            20                  25                  30

Trp Ile Gly Trp Val Arg Gln Ala Pro Gly Gln Ala Leu Glu Trp Met
        35                  40                  45

Gly Asp Ile Tyr Pro Gly Gly Gly Tyr Thr Asn Tyr Asn Glu Lys Phe
    50                  55                  60

Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Tyr Asp Phe Val Leu Asp Arg Trp Gly Gln Gly Thr Thr
            100                 105                 110

Val Thr Val Ser Ser
        115
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<210> SEQ ID NO 173
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 173

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Asp Ile Tyr Pro Gly Gly Gly Tyr Thr Asn Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Tyr Asp Phe Val Leu Asp Arg Trp Gly Gln Gly Thr Thr
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 174
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 174

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys His Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Asp Ile Tyr Pro Gly Gly Gly Tyr Thr Asn Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Tyr Asp Phe Val Leu Asp Arg Trp Gly Gln Gly Thr Thr
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 175
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 175

Gln Met Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Thr Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met

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        35                  40                  45

Gly Asp Ile Tyr Pro Gly Gly Gly Tyr Thr Asn Tyr Asn Glu Lys Phe
    50                  55                  60

Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Tyr Asp Phe Val Leu Asp Arg Trp Gly Gln Gly Thr Thr
            100                 105                 110

Val Thr Val Ser Ser
        115


<210> SEQ ID NO 176
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 176

Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
            20                  25                  30

Trp Ile Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45

Gly Asp Ile Tyr Pro Gly Gly Gly Tyr Thr Asn Tyr Asn Glu Lys Phe
    50                  55                  60

Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Tyr Asp Phe Val Leu Asp Arg Trp Gly Gln Gly Thr Thr
            100                 105                 110

Val Thr Val Ser Ser
        115


<210> SEQ ID NO 177
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 177

Asp Ile Val Met Ser Gln Ser Pro Ser Ser Leu Ala Val Ser Thr Gly
1               5                   10                  15

Glu Lys Val Thr Met Thr Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
            20                  25                  30

Glu Thr Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45

Pro Pro Lys Leu Leu Ile Phe Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

Pro Asp Arg Phe Leu Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Lys Gln
                85                  90                  95

Ser Tyr Thr Leu Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110
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<210> SEQ ID NO 178
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 178

Asp Val Val Met Thr Gln Ser Pro Ala Phe Leu Ser Val Thr Pro Gly
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
20 25 30

Glu Thr Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Lys Gln
85 90 95

Ser Tyr Thr Leu Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> SEQ ID NO 179
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 179

Asp Val Val Met Thr Gln Ser Pro Ala Phe Leu Ser Val Thr Pro Gly
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
20 25 30

Glu Thr Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr
65 70 75 80

Ile Ser Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Lys Gln
85 90 95

Ser Tyr Thr Leu Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> SEQ ID NO 180
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 180

Asp Val Val Met Thr Gln Ser Pro Ala Phe Leu Ser Val Thr Pro Gly
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
20 25 30

Glu Thr Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Ala Pro Arg Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr
65 70 75 80

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Ile Ser Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Lys Gln
                85                  90                  95

Ser Tyr Thr Leu Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110


<210> SEQ ID NO 181
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 181

Asp Val Val Met Thr Gln Ser Pro Ala Phe Leu Ser Val Thr Pro Gly
1               5                   10                  15

Glu Lys Val Thr Ile Thr Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
            20                  25                  30

Glu Thr Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45

Ala Pro Arg Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Lys Gln
                85                  90                  95

Ser Tyr Thr Leu Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110


<210> SEQ ID NO 182
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 182

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
            20                  25                  30

Glu Thr Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Lys Gln
                85                  90                  95

Ser Tyr Thr Leu Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110


<210> SEQ ID NO 183
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 183

Asp Val Val Met Thr Gln Ser Pro Ala Phe Leu Ser Val Thr Pro Gly
1               5                   10                  15

Glu Lys Val Thr Ile Thr Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
            20                  25                  30
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Glu Thr Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Lys Gln
                85                  90                  95

Ser Tyr Thr Leu Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110


<210> SEQ ID NO 184
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 184

Asp Val Val Met Thr Gln Ser Pro Ala Phe Leu Ser Val Thr Pro Gly
1               5                   10                  15

Glu Lys Val Thr Ile Thr Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
            20                  25                  30

Glu Thr Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr
65                  70                  75                  80

Ile Ser Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Lys Gln
                85                  90                  95

Ser Tyr Thr Leu Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110


<210> SEQ ID NO 185
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 185

Glu Val Gln Leu His Gln Ser Gly Pro Glu Leu Leu Lys Pro Gly Ala
1               5                   10                  15

Ser Val Arg Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Phe
            20                  25                  30

Tyr Ile His Trp Val Lys Gln Ser His Gly Lys Ser Ile Glu Trp Ile
        35                  40                  45

Gly Ser Ile Tyr Pro Asn Tyr Gly Asp Thr Ala Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Asp Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80

Met Ala Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Tyr Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser
            100                 105                 110

Val Thr Val Ser Ser
        115


<210> SEQ ID NO 186
<211> LENGTH: 119
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-continued

<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 186

Val His Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro
1 5 10 15

Gly Glu Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr
20 25 30

Asn Phe Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu
35 40 45

Trp Met Gly Ser Ile Tyr Pro Asn Tyr Gly Asp Thr Ala Tyr Asn Gln
50 55 60

Lys Phe Lys Asp Arg Phe Val Phe Ser Leu Asp Thr Ser Val Ser Thr
65 70 75 80

Ala Tyr Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Ala Arg Gly Tyr Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Thr Val Thr Val Ser Ser
115

<210> SEQ ID NO 187
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 187

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Phe
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Arg Gly Gln Arg Leu Glu Trp Ile
35 40 45

Gly Ser Ile Tyr Pro Asn Tyr Gly Asp Thr Ala Tyr Asn Gln Lys Phe
50 55 60

Lys Asp Arg Phe Val Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr
65 70 75 80

Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Tyr Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 188
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 188

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Phe
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
35 40 45

Gly Ser Ile Tyr Pro Asn Tyr Gly Asp Thr Ala Tyr Asn Gln Lys Phe

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    50                  55                  60

Lys Asp Arg Phe Val Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr
65                  70                  75                  80

Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Tyr Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr
            100                 105                 110

Val Thr Val Ser Ser
        115


<210> SEQ ID NO 189
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 189

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Asn Phe
            20                  25                  30

Tyr Ile His Trp Val Arg Gln Ala Arg Gly Gln Arg Leu Glu Trp Ile
        35                  40                  45

Gly Ser Ile Tyr Pro Asn Tyr Gly Asp Thr Ala Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Asp Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Tyr Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr
            100                 105                 110

Val Thr Val Ser Ser
        115


<210> SEQ ID NO 190
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 190

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Asn Phe
            20                  25                  30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45

Gly Ser Ile Tyr Pro Asn Tyr Gly Asp Thr Ala Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Asp Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Tyr Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr
            100                 105                 110

Val Thr Val Ser Ser
        115
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<210> SEQ ID NO 191
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 191

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Phe
20 25 30

Tyr Ile His Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ser Ile Tyr Pro Asn Tyr Gly Asp Thr Ala Tyr Asn Gln Lys Phe
50 55 60

Lys Asp Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Tyr Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 192
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 192

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Phe
20 25 30

Tyr Ile His Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ser Ile Tyr Pro Asn Tyr Gly Asp Thr Ala Tyr Asn Gln Lys Phe
50 55 60

Lys Asp Arg Phe Val Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr
65 70 75 80

Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Tyr Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 193
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 193

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Phe
20 25 30

Tyr Ile His Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

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```
Gly Ser Ile Tyr Pro Asn Tyr Gly Asp Thr Ala Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Asp Arg Phe Val Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr
65                  70                  75                  80

Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Tyr Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr
            100                 105                 110

Val Thr Val Ser Ser
        115
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<210> SEQ ID NO 194
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 194

```
Asn Ile Val Met Thr Gln Ser Pro Lys Ser Met Ser Met Ser Val Gly
1               5                   10                  15

Glu Arg Val Thr Leu Thr Cys Lys Ala Ser Glu Asn Val Val Thr Tyr
            20                  25                  30

Val Ser Trp Tyr Gln Gln Lys Pro Glu Gln Ser Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Gly Ala Ser Asn Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
    50                  55                  60

Ser Gly Ser Ala Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala
65                  70                  75                  80

Glu Asp Leu Ala Asp Tyr His Cys Gly Gln Gly Tyr Ser Tyr Pro Tyr
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105
```

<210> SEQ ID NO 195
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 195

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Gln Gly Ile Ser Gly Asp
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr His Thr Ser Ser Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Tyr Tyr Ser Lys Asp Leu Leu
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105
```

<210> SEQ ID NO 196
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 196

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Gln Gly Ile Ser Gly Asp
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Thr Pro Lys Leu Leu Ile
35 40 45

Tyr His Thr Ser Ser Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Tyr Tyr Ser Lys Asp Leu Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> SEQ ID NO 197
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 197

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Gln Gly Ile Ser Gly Asp
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr His Thr Ser Ser Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Tyr Tyr Ser Lys Asp Leu Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> SEQ ID NO 198
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 198

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Gln Gly Ile Ser Gly Asp
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr His Thr Ser Ser Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Tyr Tyr Ser Lys Asp Leu Leu
85 90 95

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Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210> SEQ ID NO 199
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 199

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Gln Gly Ile Ser Gly Asp
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr His Thr Ser Ser Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Tyr Tyr Ser Lys Asp Leu Leu
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210> SEQ ID NO 200
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 200

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Gln Gly Ile Ser Gly Asp
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr His Thr Ser Ser Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Tyr Tyr Ser Lys Asp Leu Leu
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210> SEQ ID NO 201
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 201

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Gln Gly Ile Ser Gly Asp
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Thr Pro Lys Leu Leu Ile
        35                  40                  45

Tyr His Thr Ser Ser Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
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    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Tyr Tyr Ser Lys Asp Leu Leu
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210> SEQ ID NO 202
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 202

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Gln Gly Ile Ser Gly Asp
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr His Thr Ser Ser Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Tyr Tyr Ser Lys Asp Leu Leu
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210> SEQ ID NO 203
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 203

gatgattttt tacat                                                    15


<210> SEQ ID NO 204
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 204

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1               5                   10                  15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
            20                  25                  30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
        35                  40                  45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
    50                  55                  60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65                  70                  75                  80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
                85                  90                  95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
            100                 105                 110
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Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
        115                 120                 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
        275                 280                 285


<210> SEQ ID NO 205
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 205

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1               5                   10                  15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Glu Ser Pro Asp Arg Pro Trp
            20                  25                  30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Leu Val Thr Glu Gly Asp
        35                  40                  45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Ala Ser Glu Ser Phe Val
    50                  55                  60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65                  70                  75                  80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Arg Asp Cys Arg Phe Arg
                85                  90                  95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
            100                 105                 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
        115                 120                 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Ala Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190

Ser Arg Ala Ala Gln Gly Thr Ile Glu Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205
```

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```
Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Ala Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Leu Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Pro Arg Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
        275                 280                 285


<210> SEQ ID NO 206
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 206

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1               5                   10                  15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
            20                  25                  30

Asn Pro Pro Thr Phe Ser Pro Ala Ala Leu Leu Val Thr Glu Gly Asp
        35                  40                  45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
    50                  55                  60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65                  70                  75                  80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
                85                  90                  95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
            100                 105                 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
        115                 120                 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
        275                 280                 285
```

What is claimed is:

1. A binding agent that binds programmed cell death 1 (PD1) comprising the amino acid sequences of the heavy chain complementarity determining regions (CDRs) and light chain CDRs of antibodies 122F10, 139D6, 135D1, 121G1, 127C2, 132F7, 136E10, 135C12, 136F4, or 136B4.

2. The binding agent of claim **1** wherein the binding agent is an antibody.

3. The binding agent of claim **2** wherein the antibody is a mouse antibody.

4. The binding agent of claim **1** wherein the binding agent is selected from the group consisting of an F_{ab}, $F_{(ab')2}$, $F_{ab'}$, single chain antibody, F_v, single domain antibody, monospecific antibody, bi-specific antibody, tri-specific antibody, multi-valent antibody, chimeric antibody, canine-mouse chimeric antibody, antibody comprising a canine Fc, humanized antibody, caninized antibody, and CDR-grafted antibody.

5. The binding agent of claim **1** comprising a VH comprising complementarity determining regions (CDRs) 1, 2, and 3 as set forth in SEQ ID NOS: 17, 40, and 63, respectively; and a VL comprising CDRs 1, 2, and 3 as set forth in SEQ ID NOS: 86, 109, and 132, respectively.

6. A composition comprising the binding agent of claim **1** and at least one pharmaceutically acceptable carrier.

7. A composition comprising the binding agent of claim **2** and at least one pharmaceutically acceptable carrier.

8. A composition comprising the binding agent of claim **3** and at least one pharmaceutically acceptable carrier.

9. A composition comprising the binding agent of claim **4** and at least one pharmaceutically acceptable carrier.

10. A composition comprising the binding agent of claim **5** and at least one pharmaceutically acceptable carrier.

11. The composition of claim **6** further comprising pembrolizumab.

12. The composition of claim **7** further comprising pembrolizumab.

13. The composition of claim **8** further comprising pembrolizumab.

14. The composition of claim **9** further comprising pembrolizumab.

15. The composition of claim **10** further comprising pembrolizumab.

* * * * *